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Table of Contents.

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Page.

ORIGINAL ARTICLES—
Preliminary Report on Fish Poisoning at Fanning Island (Central Pacific), by S. G. Ross, M.D. .. 617
The Anticonvulsant Properties of Creatinine, by John F. Cade 621
New Formation of Smooth Muscle in the Lung, by K. M. Bowden 623

REPORTS OF CASES—
Olivo-Ponto-Cerebellar Atrophy (Marie's Ataxia), by C. G. Lambie, Oliver Latham and G. L. McDonald 626

REVIEWS—
Anatomy for Physiotherapists 632
Dynamic Biochemistry 632
Surgical Pathology 632
Anatomical Plates 632

LEADING ARTICLES—
Radioactive Isotopes and Their Uses 633

CURRENT COMMENT—
Cerebellar Atrophy 635
Miners' Welfare in Wartime 635
A Drug for Increasing Plasma Concentrations of Penicillin 636
The Van den Bergh Reaction 637

ABSTRACTS FROM MEDICAL LITERATURE—
Bacteriology and Immunology 638
Hygiene 639

Page.

BIBLIOGRAPHY OF SCIENTIFIC AND INDUSTRIAL REPORTS—
The Results of War-Time Research 640

MEDICAL SOCIETIES—
Melbourne Pædiatric Society 642

CORRESPONDENCE—
Prefrontal Leucotomy 645
The New South Wales Branch and the Government Proposals 645
Jaundice and Hydatid Cysts 646
The New South Wales Branch Plebiscite 646

POST-GRADUATE WORK—
The Post-Graduate Committee in Medicine in the University of Sydney 646

HOSPITALS—
Centenary of the Royal Melbourne Hospital 647

NOMINATIONS AND ELECTIONS 647

MEDICAL APPOINTMENTS 648

BOOKS RECEIVED 648

DIARY FOR THE MONTH 648

MEDICAL APPOINTMENTS: IMPORTANT NOTICE .. 648

EDITORIAL NOTICES 648

PRELIMINARY REPORT ON FISH POISONING AT FANNING ISLAND (CENTRAL PACIFIC).

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SOON after my arrival at Fanning Island, in February, 1946, I was confronted with a new problem for the island—fish poisoning. No cases of fish poisoning had been recorded by previous medical officers or remembered by those people who had previously lived at Fanning. Because the number of cases has been steadily increasing, I have started an investigation into its possible cause. In this article an attempt is made to discuss this interesting as well as important problem for the population of the island.

On all tropical islands fish is the main article of food of the native population, and Fanning Island is no exception. The white population also supplements its rather monotonous diet with local fish, and when there is a shortage of meat, fish also becomes the main article of its diet.

It is well known that in the tropics there are certain species of fish which are poisonous—tetrodon or "balloon fish" is an example. It is assumed that in tetrodon the poison exists chiefly in the ovaries and testes, though it has been found also in the bile and in the liver. The natives consider that this fish is harmless when its internal organs are carefully removed and the flesh is well cleaned. They prize this "skinny" and ugly-looking fish, as soup made from it has a delicious taste.

Barracuda is another example. It may be poisonous at certain times, especially during the spawning season.

Certain species of the herring family are also poisonous in the tropics, such as *Meletta venenosa* and *Clupea venenosa* in New Caledonia, *Meletta theissa* in the West Indies and *Clupea thrissa* in Tahiti.[1]

The position with fish poisoning at Fanning Island is quite different. Except for tetrodon, no other fish was considered by the population of the island to be poisonous prior to the end of 1945, when the first cases of fish poisoning at Fanning were recorded. They were in the beginning mild, and mostly the gastro-intestinal tract was affected. Up to now ten different species of fish caught either in the ocean or in the vicinity of English Harbour area—in or close to the channel—have been responsible for fish poisoning.

From February, 1946, to April 5, 1947, there were 95 cases of fish poisoning at Fanning amongst the population of 224 people on the island; 55 patients were treated by me, and 40 cases were reported to me by native headmen as mild, recovery soon occurring without medical aid.

In this article reference will be made only to those 55 patients who were treated by me. The cases may be classified as in Table I.

When the term "whole fish" is used, it means that the fish was cooked in native fashion. Natives do not clean fish as Europeans do, but wrap the whole fish in green leaves of various kinds, mostly pandanus or palm tree, and cook it on burning coconut husks. Cooked this way it is considered by the natives as a delicacy. Only natives eat fish prepared in such a manner.

As can be seen from Table I, all cases of fish poisoning at Fanning between February and June, 1946, inclusive, belong to the group "when whole fish was eaten".

After consultation with the district officer, and taking the view that the poisonous principle, as in the case of tetrodon, might be in the internal organs, I instructed the natives to eat only fish from which all internal organs had been carefully removed, the flesh being well washed.

In spite of this advice, I saw in July, 1946, two more patients with fish poisoning, due to eating the flesh of recently caught surgeons fish or reef fish (*Hepatus* species). While the information given me about these cases may be treated with reserve, the following well-

checked case leaves no doubt that the flesh also contains the poisonous principle:

On September 19, 1946, the American army ship FS 400 arrived at Fanning from Honolulu, and was moored to a buoy about 300 yards off the ocean shore, and nearly the same distance from the entrance to the lagoon. The depth around this buoy is between 30 and 40 feet. At 3 p.m. a schnapper (*makura*), weighing about five pounds, was caught from the ship by a member of the crew, cleaned and put on ice. The flesh was fried at 4 p.m. and eaten at 5 p.m. by four members of the crew and four Chinese labourers from the cable station, who went aboard to unload the cargo.

Between four and five hours after eating the fish all eight people became ill. The illness started with epigastric pain, numbness in the limbs, tingling around the face and giddiness. Two patients also had severe vomiting, but the rest vomited only once. In about two hours after the onset several watery stools were passed by all affected.

TABLE I.

Month.	Number of Cases.	Number of Serious Cases.	When Whole Fish was Eaten.	When Only Flesh was Eaten.
1946				
February	3	2	3	0
March	1	0	1	0
April	2	1	2	0
May	1	0	1	0
June	3	2	3	0
July	2	0	0	2
August	0	0	0	0
September	8	3	0	8
October	2	1	2	0
November	2	1	0	2
December	1	1	1	0
Total, 1946	25	11	13	12
1947.				
January	8	3	6	2
February	5	2	0	5
March	8	1	0	8
April (1 to 5)	9	4	0	9
Total, 1947	30	10	6	24
Grand total	55	21	19	36

On examination of the subjects next morning the following symptoms were the most prominent: slow pulse (30 to 40 a minute), contracted pupils, sensation of tingling over the whole body, especially round the lips and at the finger-tips. A feeling of coldness when hands or feet were immersed in water at room temperature was noticed by all patients; but its first appearance was noticed six to eight hours after the onset by five persons, and twenty to twenty-four hours after by the others.

Subsequent cases and experiments on cats, dogs and domestic ducks proved beyond any doubt that the perfectly fresh flesh of several species of fish at Fanning sometimes contains a poisonous principle in the tissues, and that this poison was probably always of similar chemical structure, as in all cases the same clinical symptoms were invariably observed.

It is true that in some cases gastro-intestinal upset was more prominent than in others, in which the peripheral nervous system was more affected, but not in a single case observed were the symptoms purely gastro-intestinal.

The following is a case in which gastro-intestinal symptoms were slight, but other features were typical of those observed at Fanning Island. Its similarity with the symptoms produced by aconitine as well as by *Atriplex littoralis* (Chenopodiaceæ) is very striking.

Mr. C., a European, aged forty-three years (Case XI, 1947), reported that at 7.30 p.m. on February 2, 1947, he had eaten about three ounces of fried red schnapper (*hangamea*). This fish was caught from the ocean wharf about noon, immediately cleaned and kept on ice until cooked. The flesh was fried in beef dripping. Mr. C. went to bed at 10 p.m., but some time later (the time is unknown) was awakened by aching pains in both arms and both legs. He soon went to sleep, but about 2 a.m. (February 3) was awakened again, and found that his wife, who had also eaten the fish, was awake with similar pains. By 6 a.m. the aching pain had increased in both arms and legs, and Mr. C. went to the bathroom and commenced to wash his hands, when to his surprise he noticed a feeling of intense cold in both hands, as if he was handling ice or as if his hands had been dipped into a volatile liquid.

Examination of the hands revealed nothing visibly wrong. Cleaning of the teeth revealed that the upper jaw in particular was sore, and that the part of the face around the mouth, especially the upper lip, was tingling with "pins and needles". The drinking of water of room temperature gave an icy cold sensation in the mouth and along the œsophagus. This sensation was similar to that in the hands.

Two lots of watery fæces were passed between 6 a.m. and 9 a.m., but no vomiting was recorded. The aching sensation in the arms and legs ceased about twenty-four hours after the onset. The sensation of cold in the hands whenever they were wet, and in the mouth when water was drunk, persisted for about a week. After that it gradually became less and less and completely disappeared in a fortnight.

The patient was examined by me at 10 a.m. on February 3, and the following signs and symptoms were noticed. The pulse rate was 40 per minute, the pulse was weak but regular. The pupils were contracted. A feeling of tingling was present throughout the body, but more prominent at the finger-tips, round the mouth, on the tongue and in the throat. The sensitivity of the peripheral nervous system appeared to be diminished. No other abnormalities were noticed.

In another case the sensation of tingling around the mouth and in the legs and arms, as well as a feeling of coldness in the same parts, did not appear before twenty-four hours after the onset. Severe diarrhœa, epigastric pain and occasional vomiting were the principal symptoms right from the onset. However in this case, as in others, contracted pupils, slow pulse, low blood pressure (systolic 115 millimetres of mercury, diastolic 70 millimetres of mercury), numbness in the limbs and giddiness were present two hours after the onset.

Another interesting case of "group" fish poisoning occurred on April 3, 1947, when eight Europeans and one Chinese were affected.

The history of this case is as follows.

On April 2, 1947, between 4.30 and 5.30 p.m., a number of fish were caught in the ocean, about a quarter of a mile off shore, slightly to the north of the ocean wharf, around the place known as "Whaler Anchorage". At 6.15 p.m. the fish were taken to the kitchen of the cable station's mess, cleaned, divided into fillets and put on ice.

At 3 a.m. on April 3 Mr. McP., who was on night duty, fried a piece of greenfish (*maratea*; *Pseudoscarus* species) and ate about half a pound of it. At 6 a.m. he noticed an uneasy feeling all over his body. At 6.30 a.m. he passed the first watery stool, and at 10 a.m. he noticed tingling in both legs and at the finger-tips of both hands. At 11 a.m. Mr. McP. had a vomiting attack, but brought up nothing but a small quantity of clear stomach juice. He had eight motions altogether up till 2 p.m., when I was called in to see him. A slow pulse rate (50 per minute), contracted pupils, tingling over the body, pain in the epigastrium and weakness in the limbs were the main features found on examination. Twenty-four hours after the onset a sensation of coldness in both hands and around the mouth was noticed. Tingling and coldness were still present one week after the onset, though only in a slight degree.

Of the nine cases of this "group" of fish poisoning, seven were due to the eating of fillets from several *maratea* and two cases were due to the eating of a red schnapper (*hangamea*). In seven cases gastro-intestinal symptoms developed three to five hours after the fish was eaten; the nervous symptoms did not appear before two to six hours after the onset. In two cases nervous symptoms had been present from the onset and gastro-intestinal symptoms appeared a few hours later.

The temperature in all observed cases at Fanning has been subnormal (97·0° to 97·5° F.).

The differential leucocyte count in 15 cases revealed pronounced eosinophilia (10% to 15%), which was transitory and disappeared after about a week.

Examination of the urine in 25 cases revealed no abnormality.

Microscopic examination of fæces in ten cases revealed numerous undigested muscle fibres and some mucous shreds. No ova or parasites were seen. The colour of the fæces varied from light yellow to whitish. No bacteriological examination was carried out owing to the absence of the necessary equipment.

It is interesting to note that in those cases in which nervous symptoms were present from the early stages, after only one watery motion at the onset the patient suffered from constipation for two or three days.

A few experiments of feeding cats with suspected material were carried out. These experiments clearly indicated that the fish's muscular tissues contained the poisonous principle. They produced characteristic nervous symptoms in the animals concerned.

The following case may be quoted as typical.

On April 3, 1947, at 7 a.m., about four ounces of the flesh of a red spotted rock cod from the previous day's catch in the ocean (see above) was eaten by a female cat, eight months old. At lunch time the cat refused to take food. No abnormality in the cat's behaviour was noticed. By evening the cat was unable to walk properly, as her hind legs showed a tendency to collapse under her.

On April 4 at 7 a.m. the cat showed symptoms of paralysis of the hind legs. The paralysis became complete by evening. It was noticed that the pupils were unusually narrow.

On April 5 the paralysis had ascended to the forelegs. Severe convulsions along the spine were noticed during the day. Artificial feeding was introduced. Some difficulty in opening the cat's mouth was experienced. No vomiting or passing of a stool was observed. A teaspoonful of castor oil was given in the evening.

On April 6, early in the morning, the cat was found in the garden, where she had crawled during the night. She was unable to walk in spite of vigorous attempts. The animal looked very miserable and ill; the pupils were widely dilated. At 10 a.m. the cat passed a hard, brownish motion.

On April 7 the condition of the cat was the same. The hind legs were still paralysed. She was unable to eat or drink. Convulsions lasting two or three minutes appeared every ten to fifteen minutes.

On April 8 the cat still could not swallow any food. She could take a few steps at a time, keeping the weight of her body entirely on her forelegs. The hind legs were still paralysed, but less rigid. The convulsions had almost disappeared.

On April 9 the cat was able to walk a distance of two or three feet at a time, but then dropped suddenly. In the evening she was able to eat a small piece of raw fish for the first time since the onset.

On April 10 the cat appeared to be normal again, except for slight tremors in the body. She was able to eat, but refused to drink.

On April 11, at night, the cat gave premature birth to three dead kittens. All the symptoms of paralysis had disappeared. Though she was still weak, the cat had a good appetite and ate raw fish freely.

On April 12 the condition of the cat was normal. She jumped and played as usual, and ate and drank without difficulty.

In another case of a fully grown male dog, which was fed with raw flesh of a red schnapper (*hangamea*) (the same fish also poisoned two people), similar symptoms of ascending paralysis were observed. The dog recovered after five days, and the symptoms disappeared gradually.

Domestic ducks fed with poisoned fish also developed in eight to twelve hours paralysis of both legs lasting for several days.

Except small kittens which usually die within forty-eight to seventy-two hours after the onset, all full-grown cats and dogs used in experiments or given poisoned fish accidentally have recovered.

In general, the recovery after fish poisoning at Fanning is gradual, and general weakness persists for several weeks after specific symptoms disappear. It seems also that Europeans are more susceptible to the poison than natives.

Types of Poisonous Fish at Fanning Island.

Between February, 1946, and April 5, 1947, the following ten species of fish have been responsible for fish poisoning at Fanning (Table II).

In Table III an attempt is made to establish the classification of those fish at Fanning, which have been identified as poisonous. It is hoped that in a further communication on fish poisoning at Fanning, the scientific names of fish will be presented more accurately.

TABLE II.[1]

Name of Fish.	Number of Cases.	When the Whole Fish was Eaten.	When Only Flesh was Eaten.
Rock cod (grey)	3 (1)	1 (0)	2 (1)
Rock cod (red)	8 (5)	8 (5)	0 (0)
Black jack (*Paihere*)	8 (2)	2 (1)	6 (1)
Bonefish	5 (1)	5 (1)	0 (0)
Reef fish	5 (2)	0 (0)	5 (2)
Schnapper (*Makura*)	8 (3)	0 (0)	8 (3)
Greenfish (*Maratea*)	11 (4)	0 (0)	11 (4)
Mullet	1 (1)	1 (1)	0 (0)
Red schnapper (*Hangamea*) ..	4 (1)	0 (0)	4 (1)
(?) Bream (*Te-Kope*)	2 (1)	2 (1)	0 (0)
Total	55 (21)	19 (9)	36 (12)

[1] The number of serious cases is shown in parentheses.

There is little information available on the scientific classification of fish at Fanning, and this field is still open for an enthusiastic investigator.

For a better understanding of the whole problem of fish poisoning at Fanning, some knowledge of the habits of the fish concerned is essential. But difficulties with their classification cannot be overcome as yet, and the above information is presented with a certain amount of reserve.

TABLE III.

Names of Fish at Fanning Island Identified as Poisonous.

English.	Scientific.	Gilbertese.	Manihikian.	Hawaiian.[1]
Rock cod.	Scorpænopsis.	*Te Kuau* (grey). *Te Nikoro* (red).	*Hapuku.*	*Nohu; Okode.*
Black Jack.	? Caranx species.	*Aongo.*	*Paihere.*	*Laulí; Ulua.*
Bonefish.	Albula species.	*Te Ikari.*	*Kio-kio.*	*'O'io.*
Surgeon fish or Reef fish.	Hepatus species.	*Te Mako.*	*Uhu.*	*Paulu.*
Schnapper.	? Aprion species.	*Te Rou.*	*Makura.*	*Uku.*
Red Schnapper.	?	*Te Ikanibong.*	*Hangamea.*	?
Greenfish.	Pseudoscarus species.	*Te Karun.*	*Maratea.*	?
Mullet.	Mugil species.	*Te Aua.*	*Karehi.*	*Amaama.*
? Bream.	?	*Te Pawe.*	*Tekope.*	?
Balloon fish.	Tetrodon species.	*Te Buni.*	*Hui (Hue).*	*'O'Opuhue.*

[1] The Hawaiian names of fish are reported by Edward Y. Hosaka.[4]

Roughly, all fish at Fanning classified by me as poisonous can be divided into two groups: (i) "non-migratory" fish, which do not travel very far and normally live near one particular locality; (ii) "migratory" fish, which can travel long distances from their "nest".

The following fish belong to the first group.

1. Rock cod (grey, red spotted and blue spotted) can usually be found in shallow reef waters under rocks and in shallow caves. These fish remain in their caves until attracted by a moving object. For example, a small piece of scarlet cloth on a hook easily attracts this rather greedy fish.

2. Surgeon fish or reef fish inhabit shallow rocky shores, but are also abundant in the reefs off the ocean shores.

3. *Te Kope* (? bream) inhabit rock crevices in shallow water, near shore, around wharfs and landing places, where such protection as a pier or a pontoon is available.

All three fish normally remain in the same locality.

To the second group ("migratory" fish) belong the following specimens:

1. Black Jack (*paihere*) is a deep sea fish. However, this fish remains more or less stationary under rocks during the day, unless attracted therefrom by passing small fish, crabs, lobsters or eels; it can travel long distances at night and is found miles away from its "nest".

2. Schnapper (*makura*) and red schnapper (*hangamea*) inhabit rocky bottoms and deep places near shore. They feed close to the bottom, and crustaceans of all kinds are their principal food.

3. Green fish (*maratea*) inhabits fairly deep water for most parts of the year. With its peg-top teeth this fish picks up its food from crevices in the rocks.

4. Mullet (*karehi*) is usually found fairly close to the shore and is very fond of bays and inlets. Its principal food is seaweed and minute particles from mud and sand on the sea bottom.

5. Bonefish (*kio-kio*) prefers sandy bottoms in the lagoon and sandy holes in the reef, some distance off shore. It feeds on crustaceans and worms found on the bottom.

During my investigation on fish poisoning at Fanning I have been struck by the fact that all "non-migratory" fish, found to be poisonous, have always been caught in the same localities, the places where war material was dumped by the American army in July, 1945.

Poisonous "migratory" fish were also caught either in the same areas or a short distance from them, except a black jack (*paihere*), which was caught a few miles from the nearest dump centre.

The fact that prior to the end of 1945 no cases of fish poisoning were recorded at Fanning, and that all species of fish now known to be poisonous were eaten by the population of the island without any harm, seems to be a proof that the agent responsible for fish poisoning has recently been introduced at Fanning.

Comment.

My numerous observations since February, 1946, show that the clinical symptoms in fish poisoning at Fanning are becoming more and more severe, and that nervous features are becoming more prominent.

The fact that so many different species of fish are now poisonous and that eating any of them produces identical clinical symptoms, is another proof that the agent responsible for fish poisoning is contained in the plankton of the ocean beds and in all probability in the ocean water as well. The agent responsible for the toxicity seems to belong to the class of alkaloids, such as aconitine and strychnine, as the symptoms produced especially by aconitine are very similar to those observed at Fanning.

The only reliable information collected about the nature of the war material dumped by the American army shows that tank mines, ammunition, batteries, copper wire, other metals and all perished foods were dumped outside the entrance of English Harbour and along the ocean shores, in the vicinity of the Cable Station area. Except ammunition and mines, which were dumped some distance off shore, a lot of other material was left just on the shore and though a great deal of it has been washed away by the waves, some can still be seen on the beaches.

The fact that in the first four months after the war material was dumped there were no cases of fish poisoning at Fanning fits in with the time required for the deterioration of the metals in salty water. Also the fact that the clinical symptoms in earlier cases of fish poisoning were, as in cases of metallic poisoning, gastro-intestinal, seems to prove that the original agent responsible for the poisoning was metallic in its origin. With further deterioration of dumped war material and its absorption by plankton and algæ, poisonous food beds have been established around these places. All fish after feeding in these areas now become poisonous, because the plankton, having been for almost two years in constant contact with the emanating material, has become more and more affected by the poisonous agents.

It is interesting to note that in the case of shellfish poisoning in San Francisco, the poison was detected in and extracted from plankton.[2] Three thousand specimens of the dinoflagellate *Gonyaulex catenella* yielded one mouse unit of a poison which was found to belong to the class of alkaloids, such as strychnine, muscarine and aconitine.[2] The poison, which is heat-stable, produced clinical symptoms very similar to those observed at Fanning. The poison was also demonstrated by Sommer and Meyer, during the poison season, to be in the residue of filtered sea water.[3] A general numbness around lips, chin and cheeks was noticed in many of the San Francisco cases by Meyer and others.[3] A cat, fed with poisonous mussels, had complete posterior paralysis eighteen hours later, but recovered. Three half-grown kittens, fed with poisonous mussels in the evening, died during the night. The onset of symptoms after the ingestion of mussels in the San Francisco cases was very rapid (five to thirty minutes); in the cases observed at Fanning, the onset was considerably delayed. Otherwise the similarity of clinical symptoms is striking.

Treatment of Fish Poisoning.

Treatment consists of an immediate wash-out of the stomach in all serious cases, as well as in those in which no vomiting is present. Two tablespoonfuls of castor oil are given to an adult and between half and one tablespoonful to a child (according to age) as soon as the oil can be retained. One hour after the castor oil has been given, the following mixture is administered every three hours for two or three days: tincture of *Nux Vomica* five to ten minims, chloroform water to half an ounce.

The patient is confined to bed for at least two days with continuous application of warmth (a rubber hot-water bottle) on the epigastrium and the abdomen. Very strict diet is maintained for a few days after the onset.

Summary.

1. The fish poisoning problem at Fanning Island (Central Pacific) is discussed.

2. Between February, 1946, and April 5, 1947, 95 cases of fish poisoning at Fanning were recorded amongst the population of 224 people on the island.

3. Eating the flesh of poisonous fish, as well as eating the whole fish cooked in native fashion, produces the same clinical symptoms—slow pulse, contracted pupils, numbness and sensation of tingling over the whole body, especially round the lips and at the finger-tips. A feeling of coldness, when the body is washed in water at room temperature, is also present in the great majority of cases.

4. Gastro-intestinal symptoms (epigastric pain, diarrhœa and vomiting) are present in 75% of cases.

5. The clinical symptoms in cases of fish poisoning at Fanning are becoming more and more severe and nervous features more prominent.

6. The recovery after fish poisoning at Fanning is very gradual, and general weakness persists for several weeks after specific symptoms have disappeared.

7. Cats, dogs and domestic ducks, fed poisonous fish experimentally or accidentally, in eight to twelve hours develop ascending paralysis, lasting from three to five days.

8. Ten different species of fish have already been classified as poisonous at Fanning. Prior to 1946 these fish were eaten by the population of the island without any ill-effect.

9. Only those "non-migratory" fish which are caught in specific areas are poisonous. These areas correspond with places where the American army dumped war material in July, 1945, prior to the evacuation of the island.

10. "Migratory" fish may be poisonous if caught after feeding in the same dump centres. One case of fish poisoning has been recorded in which a "migratory"

fish, caught several miles away from any known dump centre, was eaten.

11. It is suspected that the plankton and algæ, as well as crustaceans and seaworms, on which both "migratory" and "non-migratory" fish feed, contain a poisonous principle emanating from deteriorating dumped war-material.

12. The effect of the poisonous agent at Fanning is similar to the effect of the poison isolated from sea plankton around San Francisco, where this poison was responsible for many cases of shellfish poisoning and was found to belong to the class of alkaloids.

13. The treatment of fish poisoning at Fanning is discussed.

Acknowledgements.

My thanks are due to Mr. H. Clarke for his painstaking reading and correction of this manuscript.

References.

(1) R. P. Strong: "Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases", Seventh Edition, Volume II, 1945, page 1545.
(2) H. Sommer, W. F. Whedon, C. A. Kofoid and R. Stohler: "Relation of Paralytic Shell-fish Poison to Certain Plankton Organisms of Genus Gonyaulax", *Archives of Pathology*, Volume XXIV, 1937, page 537; quoted by G. M. Dack, *loco citato*.
(3) G. M. Dack: "Food Poisoning", Fourth Impression, February, 1944.
(4) Y. Hosaka: "Sport Fishing in Hawaii", 1944.

THE ANTICONVULSANT PROPERTIES OF CREATININE.

By JOHN F. CADE,
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Introduction.

IT is necessary, first, to give an outline of the hypothesis upon which the following experimental work was based. It will be seen that the discovery of the anticonvulsant value of creatinine was an unexpected by-product of the original investigation which is still being pursued.

A reasonable assumption regarding the ætiology of manic depressive insanity is that it is analogous to thyreotoxicosis and myxœdema: mania being a state of intoxication by a normal product of the body circulating in excess, whilst melancholia is the corresponding deprivative condition. *Dementia præcox*, too, may well be a similar or identical deprivative state, its clinical difference from melancholia being due to the different personality type upon which the deficiency acts. This briefly is the hypothesis and starting point.

If this hypothesis is accepted as a working basis for investigation, it is evident that the key to the problem lies in the study of the manic patient, who *ex hypothesi* is producing the intoxicating agent in excess. If indeed this is so, it is not unlikely that, as with other substances circulating in excess, it is being excreted in the urine and may be demonstrable therein.

The first step then was to attempt to devise a method of demonstrating such a toxic agent, if it existed, in the urine of manic persons. Not knowing what the substance might be, still less anything of its pharmacology for lower animals, the best plan seemed to be to spread the net as wide as possible and use the crudest form of biological test as a preliminary investigation.

For this purpose guinea-pigs were used and fresh urine was injected intraperitoneally. From the use of concentrated urine (the early morning specimen passed after abstinence from fluid for twelve to fourteen hours) it soon became evident that some specimens of urine from manic patients were far more toxic than were any of the control specimens from normal persons, schizophrenics and melancholics. The urine from some manic subjects would kill the animals in as low a dosage as 0·25 millilitre per ounce of body weight, whereas the most toxic control specimen was not lethal in doses lower than 0·75 millilitre per ounce of body weight. So far, all that had been determined was that any concentrated urine, in sufficient quantity, would kill a guinea-pig, but that urine from a manic subject often killed much more readily.

Now the mode of death is the same in all cases, manic and control, suggesting that the same toxic agent is at work. After a latent period of twelve to twenty-eight minutes in which the animal appears perfectly well, apart from occasional initial distress of a few minutes' duration following the injection, it becomes tremulous and ataxic and in a few minutes quadriplegic, the hind legs being the first affected. It remains fully conscious and often squeals when picked up at this stage. Myoclonic twitches precede a severe tonic convulsion, and from then on the animal remains unconscious in *status epilepticus* of tonic type with convulsive respiratory gasps until its death a few or many minutes later. An occasional animal recovers.

To determine the actual toxic agent the principal nitrogenous constituents of urine were first investigated. It was not very surprising to find that urea was the guilty substance. In a 4% solution in water, its lethal dose for guinea-pigs was 1·0 to 1·25 millilitres per ounce of body weight—a relatively enormous dose, roughly equivalent to 100 grammes in a ten stone man. The mode of death was exactly the same as with urine. An interesting point is that there appear to be no intermediate effects—the animal either develops no symptoms whatever following the injection, or it dies. Uric acid 0·1% in normal saline solution and creatinine 0·1% in normal saline solution appeared to have no toxic effects at all when injected intraperitoneally in maximal doses. It is mechanically impossible to inject more than about two millilitres of fluid per ounce of body weight into the peritoneal cavity of a guinea-pig, especially the half-grown male animals which were mostly used.

Although the actual toxic agent was identified, this was by no means a complete explanation of what happened when urine was injected, as certain quantitative relationships were far from being fulfilled. For example, some specimens from manic subjects were lethal in doses of 0·25 to 0·5 millilitre per ounce of body weight. As the lethal dose of 4% urea solution is one millilitre per ounce of body weight, one would have to postulate an impossible concentration of 8% to 16% of urea in these specimens.

TABLE I.

Solution.	Minimal Lethal Dose in Millilitres per Ounce of Body Weight.
1. Urea 4% solution in water	1·0
2. Uric acid 0·1% in normal saline	Not determinable
3. Creatinine 0·1% in normal saline	Not determinable
4. Urea 4%, Uric acid 0·1% in water	0·75
5. Urea 4%, Uric acid 0·1%, Creatinine 0·1% in water	2·2
6. Urea 4%, Creatinine 0·025% in water	2·0
7. Urea 4%, Creatinine 0·2% in water	2·0

It therefore became necessary to determine what substances modified the toxic effect of urea, either by diminution or by enhancement. The results are summarized in Table I. It will be noted that uric acid has a slightly enhancing effect.

The Protective Action of Creatinine.

The most surprising result obtained, however, was the remarkable protective action of creatinine against the toxic effect of urea. The minimal lethal dose of an

aqueous solution of creatinine 0·025% and urea 4% was double that of a solution of urea 4% (Table I). It will be seen that the same degree of protection was afforded by a fairly wide range of creatinine concentration—0·025% gave as much protection as 0·2%. It is to be noted also from Table I that creatinine more than counterbalanced the mildly enhancing toxic effect of uric acid.

In view of its protective value against the lethal convulsive action of urea on the central nervous system it was decided to find out if creatinine had any wider anticonvulsant effect.

Its effect on the convulsions induced by pentamethylenetetrazol ("Cardiazol", "Phrenazol" or "Pentazol") was determined. This drug in 10% solution in a dosage of one-quarter minim per ounce of body weight in four animals produced merely mild transient myoclonic twitching, commencing one to two minutes after intraperitoneal injection and lasting for several minutes.

A dosage of half a minim per ounce of body weight killed all of six animals. In one to two minutes there was severe myoclonus quickly developing into a furious clonic fit. The animals then went into *status epilepticus* of clonic type and died three-quarters of an hour to three hours later.

In twelve animals an intraperitoneal injection of 9·5% aqueous solution of creatinine in a dosage of one millilitre per three ounces of body weight was given twenty to twenty-five minutes before the lethal dose of half a minim of convulsant per ounce of body weight.

The results were as follows. On three animals there was no discernible effect. In one animal a slight clonic fit occurred half an hour after injection, with twitching for five minutes and then no discernible effect. One animal developed severe myoclonus and several clonic fits (but no *status epilepticus*), practical recovery occurring in twenty-five minutes. In one animal *status epilepticus* occurred with commencing recovery in one and a half hours and complete recovery in three hours. The remaining six animals died in *status epilepticus*.

Thus there was a 50% reduction in mortality with a 25% complete suppression of convulsive phenomena.

Considering the relatively enormous dose of convulsant employed (corresponding approximately to 70 millilitres of "Cardiazol" in a ten stone man), these experimental results seemed to offer sufficient warrant for a clinical trial of creatinine in epilepsy in man.

Creatinine itself appears to have no toxic effect even in comparatively huge doses. As much as ten millilitres of a 9·5% aqueous solution of creatinine was injected into a twelve and a half ounce animal with no discernible action.

A Toxic Factor in Urine.

The idea of a toxic factor in urine is not relevant to the use of creatinine as an anticonvulsant, but it is of theoretical importance in the pursuit of the original investigation.

It was thought at first that the extra toxic effect of some specimens of urine from manic patients might be explicable on the basis of a high excretion level of urea or uric acid, or of a low level or absence of excretion of creatinine; but when quantitative urea and creatinine estimations were carried out (urea by the hypobromite method, creatinine by Folin's colorimetric method with alkaline picrate solution) it was found that urine from manic subjects did not differ significantly from other urine in urea or creatinine content. The toxicity of some specimens was such that it could not be explained on the assumption that the creatinine effect had been simply neutralized. It was more than that. The specimens were more toxic than could be explained by the concentrations of urea actually present even if it were being enhanced maximally by uric acid. One would have required a urea concentration of 8% to 16%.

It is difficult to avoid postulating a third substance in urine which more than neutralizes the protective action of creatinine against the toxic activity of urine.

Briefly then the following factors are operative: (i) the toxic effect of urea; (ii) the protective effect of creatinine; (iii) a third toxic substance which (*a*) neutralizes the protective effect of creatinine and (*b*) enhances the toxic effect of urea.

The urea and creatinine concentration of urine being known, a calculated minimal lethal dose can be worked out, on the assumption that no other factors are involved. The actual minimal lethal dose is then determined and the ratio of the calculated minimal lethal dose to the actual minimal lethal dose is a measure of the presence of the third factor.

In bulk specimens of urine from manic subjects, which are considerably less toxic than some single morning specimens, this ratio has in general a numerical value of two to four, that is, the actual minimal lethal dose is two to four times less than the calculated dose.

Creatinine in Epilepsy.

Clinical evaluation must be on an extremely limited scale at the present time owing to the high cost of creatinine and the great difficulty in obtaining a sufficient quantity for even short periods of adequate dosage. It is of no use to choose patients with infrequent fits, as creatinine would have to be given over too long a period for results to be accurately assessed. One must choose patients who are having fits almost daily in spite of previous treatment, missing at the most one, two or three days between major fits. Even in a large mental hospital it is often difficult to find suitable patients.

The first patient upon whom creatinine was tried was a man, aged thirty-five years, who had been having fits since the age of eighteen years and who was averaging approximately six major fits a week, most of them at night. Previous combinations of drugs had had little or no effect on the number of fits.

"Dilantin" had been tried in adequate dosage some months previously with no result and had been discontinued. Since that time he had been on a constant dosage of sodium phenobarbital, one and a half grains, twice a day. This was continued without alteration of dosage throughout the fortnight of creatinine treatment.

The problem of dosage had to be worked out upon him. For a start it was thought, on the basis of a normal daily excretion of one to one and a half grammes of creatinine, that nine grammes daily in three equal doses at 7.30 a.m., 1.30 p.m. and 7.30 p.m. might produce an adequate blood concentration. At the end of four days he had had two fits, on alternate nights. Dosage was increased to twelve grammes daily, the extra three grammes being given at 10.30 p.m. By the end of a week of this extra dosage he had had only three fits, which was a 50% reduction on the average for the previous nine weeks.

On the twelfth, thirteenth and fourteenth days, as enough creatinine was not available, the two first doses of the day were reduced from three grammes to one and a half grammes, with the result that on the thirteenth and fourteenth days the patient commenced to have fits during the day, an unusual event for him. It appeared that the night dosage was almost adequate, as he had had a record period (for him) of four successive nights free of fits, but that with the reduced day dosage he was "escaping".

It was evident, as far as dosage was concerned, that less than nine grammes daily would probably not be worth giving, and it was decided that future trials would consist of 12 to 16 grammes daily in four doses.

The results of this first trial (see Figure I), though not dramatic, were encouraging for the following reasons. (i) Instead of two to three nights free of fits in each of the preceding five groups of twelve nights, he had seven free nights. (ii) The total number of fits was five for this twelve-day period, compared with the previous average of ten. (iii) The most suggestive evidence of the value of creatinine is seen, however, in the well marked "release" phenomenon, well shown in Figure I. The fact that after reduction of the day dosage on the twelfth day he had four fits in daylight hours (two on the thirteenth, two on the fourteenth) was very suggestive of an escape from control and similar to the usual increase in fits when an effective drug is suddenly withdrawn. On the first two days following cessation of creatinine he had three and six fits respectively before settling down to his usual single nocturnal fit.

Further clinical results are slowly in the process of accumulation as sufficient creatinine becomes available from time to time.

Significance of Results.

In view of its anticonvulsant properties it appears important to assess the role of creatinine in the physiology and pharmacology of the central nervous system. How widespread, for example, is its protective role? In this connexion, its effect on the course of poisoning by tetanus toxin was determined in guinea-pigs. The toxin was

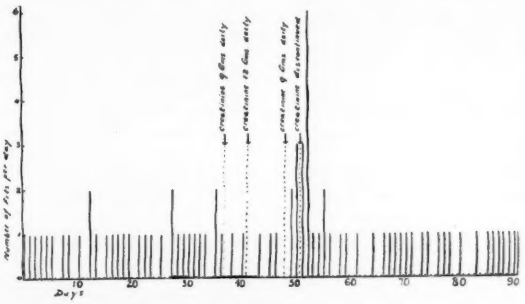

FIGURE I.

Results of treatment of epileptic subject with creatinine. Sodium phenobarbital (three grains daily) was given throughout.

provided by the Commonwealth Serum Laboratories and contained five minimal lethal doses per millilitre. The individual dose was made up to two millilitres for each animal and given subcutaneously into the groin.

Twenty-five guinea-pigs were used in five groups of five animals.

Group I was given one minimal lethal dose of toxin and no creatinine.

Group II was given one minimal lethal dose of toxin, followed by two millilitres of 9·5% aqueous solution of creatinine subcutaneously on commencement of symptoms.

Group III was given one minimal lethal dose of toxin, with two millilitres of 9·5% solution of creatinine subcutaneously every twelve hours, the first injection at the same time as the toxin.

Group IV was given two minimal lethal doses of toxin with creatinine as for Group III.

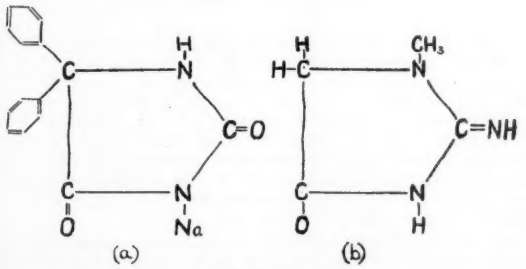

FIGURE II.

Structural formulæ of (a) "Dilantin" and (b) creatinine.

Group V was given five minimal lethal doses of toxin with creatinine as for Group III.

The results can be stated very briefly. All animals died within three days and there was not the faintest evidence that creatinine favourably influenced the course of the poisoning. It seemed, in fact, to hasten death in Group II and the last animals to die were two from Group I.

It is of interest to note the likeness that exists between the structural formulæ of creatinine and "Dilantin" (sodium diphenyl hydantoinate) (Figure II).

Merritt, Putnam and Schwab[1] started with the observation that phenobarbital was far more effective as an anticonvulsant in epilepsy than other barbiturates. They thought that the phenol fraction might explain the difference and investigated various compounds containing the phenol ring. A number, of which the most potent was "Dilantin", were found to be efficient anticonvulsants. Merritt and Putnam showed that hydantoin itself produced little or no elevation of the convulsive threshold, and their attempt in another paper to correlate molecular configuration with anticonvulsant effect was a complete failure.

The question now arises whether the effectiveness of "Dilantin" is not due to its similarity to creatinine, to its alteration to creatinine in the body, or to its stimulation of overproduction of creatinine or creatine. In connexion with this last postulate Beard[2] states that the ingestion of creatinine in rats and man greatly stimulates the formation of creatine and creatinine.

In spite of the notorious fallacy of attempting to argue from chemical structure to pharmacological effect it would be extremely interesting to determine the anticonvulsant properties of diphenyl creatinine.

Acknowledgements.

My thanks are due to Dr. J. Catarinich, Director of Mental Hygiene, for every assistance in the difficult task of procuring sufficient creatinine; to the medical and laboratory staff of the Mental Hospital, Mont Park, for their cooperation in the collection of necessary specimens and the supply of laboratory animals; to Mr. F. J. Boyd, pharmacist at Mont Park, who has been untiring in his preparation of the various solutions required; and finally to Dr. F. G. Morgan, the Director, and Mr. Patterson, of the Commonwealth Serum Laboratories, who kindly supplied the tetanus toxin used.

References.

(1) H. H. Merritt and T. J. Putnam: "A New Series of Anticonvulsant Drugs Tested by Experiments on Animals", *Archives of Neurology and Psychiatry*, Volume XXXIX, 1938, page 1003.
(2) H. H. Beard: "Creatine and Creatinine Metabolism."

NEW FORMATION OF SMOOTH MUSCLE IN THE LUNG.

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In the normal bronchial tree smooth muscles run in all directions in the layer next to the mucosa. This muscle layer remains distinct to the end of the respiratory bronchioles. Smooth muscle is also found in the walls of the alveolar ducts and between the mouths of the alveolar sacs, where it mingles with the elastic and collagenous fibres. It has been claimed that thin wisps of smooth muscle are also distributed over the alveolar walls, although these wisps are very difficult to demonstrate. Their presence in this situation is denied by most investigators. Elsewhere in the lung, apart from the blood vessels, smooth muscle fibres are not as a rule seen.

The smooth muscle tissue of the bronchial tree is derived in the embryo from the mesenchyme surrounding the bronchial buds. Into this mesenchyme the primitive lung buds grow, and there they undergo repeated division. In those places in the bronchial tree where smooth muscle will develop, the mesenchymal cells stretch out, their nuclei elongate, and thin fibrils appear in the cytoplasm. The mesenchymal cells thus become muscle cells. That smooth muscle cells retain the ability in the fully developed state to divide by mitosis follows from observations of unquestionable regeneration of smooth muscle in the human body. Regeneration of smooth muscle, although it does definitely occur, is, however, usually regarded as uncommon, for when this type of muscle is injured or destroyed, repair by fibrous tissue predominates, and the

evidence of muscle cell proliferation is scanty, even when looked for with care.

However, there are some pathological conditions in the lung in which new smooth muscle may be found even in large amounts away from the sites of its normal distribution. Curiously enough, there is very little mention of this condition in textbooks of pathology.

Davidsohn[1] described a case of carnification of the lungs of an adult male, in which so much new muscle substance was found in the carnified tissue that he used the term "muscular cirrhosis" to describe it, in contradistinction to the ordinary "fibrous cirrhosis". That the carnification in this case was actually due to muscle tissue was confirmed by the staining of sections with Van Gieson's stain. In these sections interlacing bundles of smooth muscle in disorderly array somewhat resembled a uterine myoma. Davidsohn reviews the literature and states that previous investigators had drawn attention to the new formation of smooth muscle in some pathological lung states and speculated on its ætiology. The opinion had been previously expressed by various writers that the new formation of smooth muscle fibres in the lung was due

FIGURE I.

Muscular scar formation in lung. Extensive proliferation of smooth muscle tissue.

to hyperplasia of preexisting smooth muscle fibres. Orth[2] found new formations of smooth muscle fibres and stressed their appearance in brown induration of the lung.

The condition has also been described by Eberth[3] in siderosis, and Tanaka[4] saw it also in syphilitic lungs.

Kaufmann[5] states that in sections of lungs which on macroscopic examination looked like examples of common carnification, he saw pictures analogous to the muscular cirrhosis described by Davidsohn; the starting point of the muscle fibre strands from small bronchi could be plainly demonstrated in Kaufmann's cases.

The condition of lobar pneumonia is usually followed by resolution, but occasionally organization of the intra-alveolar exudate may occur, with the conversion of the greater part of the affected lung into fibrous tissue. In rare cases smooth muscle fibres participate in this process of organization. Oertel[6] draws attention to this finding and makes the following observation:

> In the ordinary course of events, the growth of granulation tissue is the joint contribution of all these mesodermal elements of a district, which grow as a unit, and not as a fusion of separate parts from different sources.

This condition of new formation of smooth muscle fibres I have frequently observed in the lungs in cases of long-standing bronchiectasis, when they were specially looked for, and in sections stained accordingly.

The best example of smooth muscle proliferation that I have seen in the lung was in one case of brown induration accompanying severe rheumatic heart disease. In this particular specimen microscopic examination showed myriads of little smooth muscle bundles present in the thickened interalveolar walls.

In bronchiectasis, when chronic infection has been of long duration, examination of the extrabronchial tissue frequently reveals marked pathological change. Examination of these areas, special stains being used for smooth muscle, sometimes shows a surprising amount of newly formed muscle tissue. This appears to be related to the long-standing chronic inflammation and not to the bronchiectasis *per se*. In some cases the origin of this new muscle tissue can be traced to the affected bronchi; sometimes direct continuity exists between the muscle of the bronchial wall and that in the scar tissue replacing lung parenchyma.

In cases of bronchiectasis, in which a large amount of inflammatory destruction of the lung parenchyma occurs,

FIGURE II.

Showing thickened interalveolar walls containing a large amount of smooth muscle tissue.

instead of the usually formed connective tissue, bundles of muscle fibres may be richly developed in the scar tissue; indeed, the new tissue replacing the destroyed lung may consist almost entirely of muscle fibres—a sort of muscular scar formation at the site of perished lung parenchyma. On the other hand, in those cases in which the lung parenchyma has not been destroyed to any great extent, considerable thickening of the interalveolar walls may be seen, and this interalveolar tissue is sometimes rich in smooth muscle cells.

The first illustration is from a lung, examination of which revealed bronchiectasis with pronounced chronic inflammatory changes, collapse and gross fibrosis of lung tissue. The first photomicrograph (Figure I) shows an astonishing amount of new muscle tissue. Here, as in Davidsohn's case, an interstitial proliferation has occurred, richly interspersed with muscle fibres. This is a good example of "muscle scar formation" replacing destroyed lung parenchyma. The illustrative section shows no orderly arrangement, the muscle cells are, for the greater part, grouped in bundles of various size, irregularly disposed in criss-cross fashion. No continuity could be demonstrated between the new muscle tissue and that of the bronchi or blood vessels. Some of the muscle cells were much longer and of much greater diameter than normal. No definite mitotic figures were seen, although

some of the cells appeared to possess two nuclei. In the less affected areas the alveoli have undergone various changes and some of them are represented by gland-like structures which result from the flattened epithelial cells becoming cubical in form. In other areas adipose tissue was found. This tissue is never seen in normal lungs, but occurs occasionally in chronic inflammatory conditions.

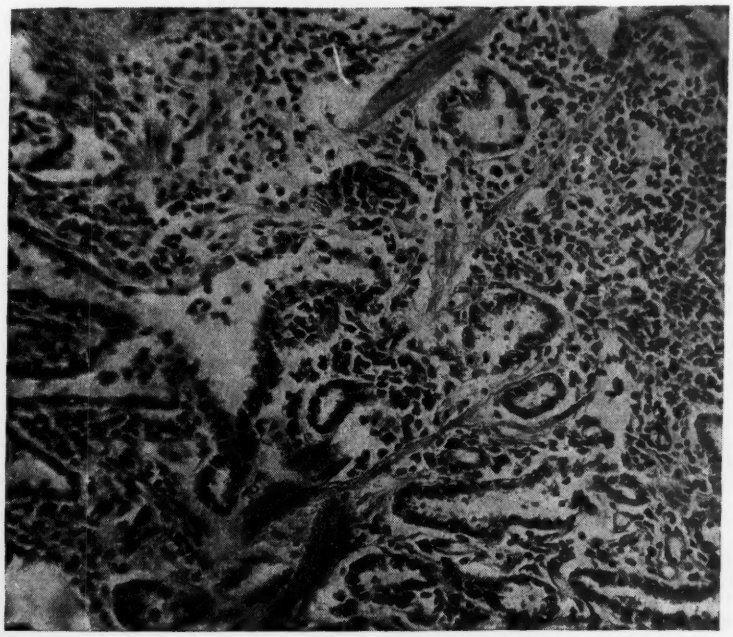

FIGURE III.—Showing a few muscle bundles. Marked epithelial activity. Reticulo-endothelial hyperplasia.

In other cases, in which the lung is less severely affected by inflammation, thickening of the inter-alveolar walls is the principal change seen, and the interalveolar tissue may contain many smooth muscle strands and fibres. This condition is illustrated in Figure II; the section was prepared from a lung affected by long-standing bronchiectasis. The muscle cells may easily be confused with fibroblasts, unless special stains are used in their differentiation. In the sections studied, Masson's method, as modified by Goldner,[7] was used to stain muscle cells red and fibrous tissue green. In this way what were at first sight thought to be patches of fibrous tissue sometimes proved to be muscle, and groups of muscle cells were demonstrated amongst fibrous tissue, distributed in a manner analogous to the muscle cells in the fibrous tissue septa of the spleen. In Figure II there are both emphysema and a considerable thickening of the inter-alveolar walls, which contain a relatively large proportion of irregularly disposed muscle cells, some of them grouped in bundles. Well-marked epithelial proliferation is also present, the epithelial cells having taken on a cubical form.

The condition is also well demonstrated in Figure III, prepared from another adult lung, the seat of long-standing bronchiectasis. Patches of smooth muscle are evident in the interstitial tissue. Here also, pronounced epithelial activity has taken place; epithelial cells line alveolar-like spaces. The alveoli have been converted into gland-like structures, similar to those seen in the embryonic lung. In addition, considerable hyperplasia of the reticulo-endothelial tissue is observed. The same appearance is evident in Figure IV, in which again much smooth muscle is present, embedded in fibrous tissue.

Discussion.

That proliferating muscle fibres are found in a variety of conditions, not all with an inflammatory basis, suggests that there may be more than one ætiological factor.

What is the origin of this smooth muscle? In the first place it is not a true neoplastic process. Though the proliferation of muscle and fibrous tissue may produce a focal resemblance to myomatous tissue, there is no local proliferative mass suggesting true tumour formation displacing or invading the lung tissue. In some cases the origin of the new muscle can be traced to the proliferating smooth muscle of the affected bronchial walls. Occasionally, patches of smooth muscle may be seen in sections of lung,

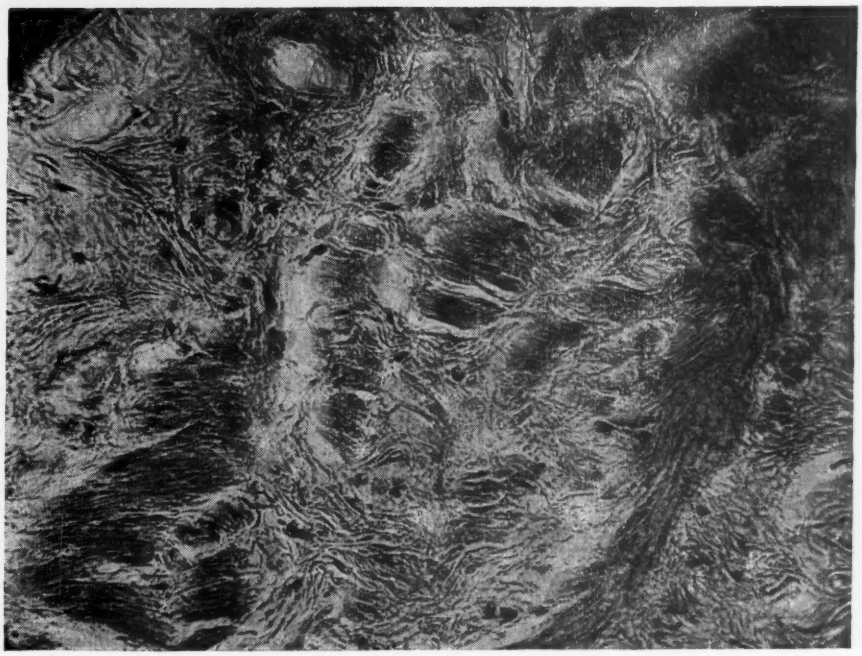

FIGURE IV.—New formation of smooth muscle embedded in fibrous tissue.

the result of tangential cutting of the walls of blood vessels. These are readily distinguishable and serial sections will soon demonstrate the origin of these muscle fibres. The muscle tissue which has been described and illustrated has no relationship to blood vessels.

According to some authors, the walls of the alveoli in the adult lung consist primarily of a very dense network of anastomosing capillaries, accompanied by scattered perivascular cells, probably of mesenchymal origin. If these cells are mesenchymal, it is possible that the new muscle cells may be derived from them. In speaking of smooth muscle cells, Maximow and Bloom[9] stated that "it is practically certain they may develop from the perivascular embryonic cells of the adult". It has not been conclusively proved that these perivascular cells are of mesenchymal origin. Their epithelial origin has not been disproved, and the weight of evidence seems to indicate that these cells are really epithelial.

Sometimes the connective tissue cells of the body in their multiplication do not reproduce the same type of cell but those of another connective tissue. Most of the connective tissues of the body are differentiated and in their multiplication reproduce the same type of cell. Nevertheless, the assumption of osteoblastic functions by connective tissue cells quite away from original osteoblasts does occur, and certain other lapses from strict specificity may be observed. Specialization among the connective tissue cells is not so rigid as in the higher tissues. In the walls of the bronchi, and indeed in the lung parenchyma, we see sometimes true bone formation with bone marrow, a lapse from true specificity. In the cases under discussion it is conceivable that, given the appropriate stimulus, connective tissue cells have assumed the function and form of myoblasts, just as mesoblastic cells assume the function and form of osteoblasts.

Completely developed smooth muscle cells in the adult have the ability to divide by mitosis to a certain degree as has been observed in the vicinity of injured muscle. Here, instead of repair by fibrous tissue, true regeneration of smooth muscle occurs. It is possible then that the new smooth muscle described in these cases originates from preexisting muscle fibres by the division and proliferation of the latter.

Summary.

The normal smooth muscle in the lung is first described. Reference is made to some pathological conditions in the lung in which new smooth muscle makes its appearance away from its normal sites.

New formation of smooth muscle is described in the lung in cases of bronchiectasis in which there has been infection of long duration.

Four examples of the condition are illustrated and described.

Acknowledgement.

I wish to acknowledge my indebtedness to Professor P. MacCallum for his assistance in this work.

References.

(1) C. Davidsohn: *Berliner klinische Wochenschrift*, Volume II, 1907, page 33.

(2) J. Orth: *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medicin*, Volume LVIII, 1873, page 126.

(3) C. J. Eberth: *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medicin*, Volume LXXII, 1878, page 96.

(4) T. Tanaka: *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medicin*, Volume CCVIII, 1912, page 429.

(5) E. Kaufmann: "Pathology for Students and Practitioners", 1929, Volume I, page 400.

(6) H. Oertel: "Special Pathological Anatomy", 1938, page 241.

(7) J. Goldner: "Modification of Masson Trichrome Technique for Routine Laboratory Purposes", *The American Journal of Pathology*, Volume XIV, 1938, page 237.

(8) A. Maximow and W. Bloom: "Text Book of Histology", 1934, page 37.

Reports of Cases.

OLIVO-PONTO-CEREBELLAR ATROPHY (MARIE'S ATAXIA).

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IN a series of papers published between the years 1863 and 1876 Friedreich differentiated the form of ataxia which bears his name from locomotor ataxia, which had been described by Duchenne de Boulogne in 1858-1859. Duchenne's description of the clinical features of locomotor ataxia is ranked as one of the classics of medicine; but with regard to the underlying pathological anatomy, he attributed the condition to a cerebellar lesion and overlooked the importance of degenerative changes in the cord. It was Friedreich who first pointed out the relationship between ataxia and degeneration of the posterior columns, and he drew attention to earlier cases of what appear to have been locomotor ataxia (Cruveilhier, 1835-1842; Ollivier, 1837; Stanley, 1840), in which such degeneration was found. Syphilis also figures largely in the records of these cases. Friedreich indicated several of the points in which the signs of his form of ataxia differ from those of Duchenne's ataxia, namely, in the absence of disturbances of touch and pain sensation, of sight, of ocular movements (except nystagmus) and of the bladder, and in the presence of speech defect and nystagmus. Friedreich emphasized the familial incidence of the disease, its appearance at an early age and the absence of any relationship to syphilis. With regard to the pathological anatomy, he described the degeneration of the posterior columns, of the dorsal and ventral cerebellar tracts and of Clarke's column.

Friedreich's ataxia was the first of the hereditary abiotrophies of the nervous system to be clearly distinguished. The next landmark in the history of our knowledge of the ataxias and abiotrophies of the nervous system was the differentiation of hereditary cerebellar ataxia from Friedreich's ataxia by Pierre Marie in 1893. Marie based his conclusions upon data provided by cases previously reported by Fraser (1880), by Nonne (1891), by Sanger Brown (1892), and by Klippel and Durante (1892). He pointed out that hereditary cerebellar ataxia differed from Friedreich's ataxia in its later age of onset (twenty to thirty years), in the exaggeration of the knee jerks, in the frequency of spastic phenomena and in the absence of deformities such as spinal curvature and *pes cavus*. The essential features of the ataxia described by him are incoordination of combined cerebellar type (staggering gait, intention tremor, nystagmus, and slow, slurring, explosive or scanning speech) and familial incidence. However, he mentions certain other characteristics—spasmodic muscular contractions, exaggerated facial movements, muscular rigidity and occasionally contractures, paræsthesiæ, visual disturbances (impairment of visual acuity and dyschromatopsia due to optic atrophy), paralysis of ocular muscles and pupillary changes—some of which (for example, ocular disturbances and paræsthesiæ) are probably not essential to the syndrome. Some of these features would indicate a more widespread distribution of lesions than is implied in the simple term cerebellar atrophy. With regard to the pathological basis of the syndrome, Marie—citing Fraser's and Nonne's cases—mentions only cerebellar atrophy, with diminution in volume of the grey matter of the cerebellar cortex and degeneration or disappearance of the cells of Purkinje. At the time when Marie wrote, no autopsies had been performed in the cases of Sanger Brown and of Klippel and Durante, and the lack of correlation between clinical findings and pathological anatomy probably led him to include more than was warranted in a single

pathological entity. Subsequently Adolph Meyer (1897) performed an autopsy upon the sixth patient of Sanger Brown, and found doubtful atrophy of the cerebellum and changes in the spinal cord resembling those of Friedreich's disease. Lewellys Barker (1903) also made post-mortem examinations on two members of the same family, with somewhat similar findings but with some evidence of degenerative changes in the olives. It would appear that part of the confusion about the definition of hereditary cerebellar ataxia is due to the existence of transition forms between this disease and Friedreich's ataxia, or of combinations of the two conditions, as has been maintained by several authors (Mingazzini, 1905-1906; Nonne, 1905; Raymond, 1905; Seiffer, 1902; Bing, 1905; Wernicke, 1903; and Marie himself and his pupil Londe, 1895). Into this category would come the above-mentioned cases of Sanger Brown, and those of Schultze (1887), of Menzel (1891), of Seeligmüller, of Seiffer (1902), of Mingazzini and Perusini (1904), of Mingazzini (1905), of Nonne (1905) and others. Seiffer (1902) suggests that the two diseases should be brought into one category—namely, familial ataxia, of which Friedreich's ataxia is the spinal and Marie's the cerebellar form. Nonne (1905) cites the case of two brothers, one of whom had the spinal and the other the cerebellar form.

Not only is there evidently a close relationship between Friedreich's ataxia and hereditary cerebellar ataxia, but Marie speculates upon the possibility of bringing together these diseases and the form of familial cerebral diplegia described by Freud in 1893. Taking all these observations together, he suggests that the hereditary degenerative process may strike not only at one part, but simultaneously at several organically related or distinct parts of the central nervous system, and thus accounts for the divers clinical pictures which may be encountered.

Greater clarity has been introduced into this nosographical problem by the work of Dejerine and Thomas (1900), who described two cases in which incoordination of cerebellar type similar to that described by Marie was found at autopsy to be correlated with the presence of degeneration of the olives, of the arcuate nuclei, of the pontine nuclei and of the cerebellar cortex. To this syndrome they applied the term "olivo-ponto-cerebellar atrophy". They did not regeard the condition as identical with Marie's hereditary cerebellar ataxia, because of its later age incidence (fourth to sixth decade) and the absence of any family history of the disease. However, cases of olivo-ponto-cerebellar atrophy have been reported (Keiller, 1920) in which there was well-marked evidence of hereditary transmission, so that the cases of Dejerine and Thomas and of Loew (1903) would appear to represent sporadic instances of the affection. For this reason Hassin and Harris (1936) regard Marie's ataxia and olivo-ponto-cerebellar ataxia as belonging to one pathological process.

While Dejerine and Thomas described olivo-ponto-cerebellar atrophy as consisting in a simultaneous degeneration of the cerebellar cortex and of the olives, the arcuate nuclei and the pontine nuclei, Hassin and Harris (1936) consider that the degeneration of the nuclei situated in the medulla and pons and of the fibres proceeding from them to the cerebellum by way of the inferior and middle cerebellar peduncles is primary—the degeneration of the cerebellar cortex being secondary and due to retrograde transsynaptic degeneration of the Purkinje and other cells of the cerebellar cortex. There is, however, no evidence that such transsynaptic degeneration can occur. Winkler (1923), Bakker (1924) and Hassin and Harris (1936) have expressed the view that the condition is primarily an abiotrophy of the cell groups (above-mentioned) derived from the rhombic lip, the development of which has been described by Essick (1907, 1912). However, further light appears to have been thrown upon the origin of the structures involved in Marie's ataxia by the recent work of Cooper (1946) on the derivatives of the basal plate. This will be further discussed below.

Although olivo-ponto-cerebellar atrophy is associated with the names of Dejerine and Thomas, earlier descriptions of the disease may be found in the literature—for example, those of Royet and Collet (1893), of Pierret (1872), and of Combette (1831).

The reports of Marie and of Dejerine and Thomas both mention rigidity as a minor characteristic of the syndromes they describe, and Hassin also reports that in one of his cases rigidity and tremor developed in the later stages; but in some cases this feature comes to dominate the whole clinical picture. This was so in the cases described by Ley (1924-1925) and by Guillain, Mathieu and Bertrand (1926), and also in the case which is the object of the present study. The rigidity may be of such a type and degree as to cause the patient to exhibit an appearance resembling that of Parkinson's disease. Guillain, Mathieu and Bertrand (1926) could not find sufficiently marked changes in the basal ganglia to account for the condition, and they attempted to explain it on the basis of disturbed cerebellar function.

In the present case there were some scattered lesions in the caudate nucleus, putamen, *globus pallidus* and *substantia nigra*, but perhaps hardly sufficient to account for the symptomatology. In the light of recent investigations by Wyke and McGovern (personal communication) on the rigidity-tremor syndrome in dogs, it appears to be significant that in the present case the maximal changes were localized in the posterior portion of the palæocerebellum. Animals having lesions predominantly in this situation may exhibit rigidity with flexion. That lesions of the posterior portion of the palæocerebellum may play a part in the production of rigidity in flexion is also suggested by the experimental work of Moruzzi. It is already known that lesions of the anterior portion of the palæocerebellum cause rigidity in extension.

Clinical Record.

The patient, E.N., aged fifty-nine years, was admitted to the Royal Prince Alfred Hospital on August 10, 1945. Conscious on his admission, he lay quietly in bed but was unable to speak except by muttering unintelligibly, so that the history had to be obtained from his wife and from available records. Apart from the operations of appendicectomy and herniorrhaphy during the 1914-1918 war, a "cardiac neurosis" following a strain at work in 1936, and a transurethral resection of the prostate in 1939, he had been well until March 16, 1942. On that day, while at work, he was run into by a tractor, which pinned him against a bench and fractured his left tibia. He was put to bed with the injured leg in splints for a few days and then in a plaster cast. On the third night after this accident he appeared to have a nightmare and became very restless, complaining of pain in the right side of the head. The following morning he was seen by his wife to be paralysed on the left side, his face being "all screwed up" and his chin twisted to the right. His speech was jumbled for the first twenty-four hours, but had improved by the following day. He passed blood in the urine once that day, but never again, and he complained of double vision for five or six weeks from that date. He was attended by doctors for his fractured leg about this time, but no mention was made of any other symptoms; moreover, it is curious that none of the doctors who examined him noticed any abnormality other than his injury. However, his condition gradually improved, and in about a week he was walking with the aid of a stick, his left lower limb in plaster.

On August 24, 1942, he was examined by Dr. Gilbert Phillips who reported as follows:

> The pupils are central, circular and equal and react to light. There is no ptosis nor proptosis. He complains of diplopia, but the external ocular movements are full and there is no nystagmus. Both left and right optic disks are normal. There is no facial weakness and the expression is mask-like. The tongue is tremulous and there is a coarse tremor of the outstretched hands. The tendon reflexes are normal in the right upper extremity, but increased in the left, with definite cog-wheel rigidity. The ankle jerk is of the spastic type on the left side, but normal on the right. He exhibits a tendency to festination and retropulsion.
>
> This is an obvious case of Parkinsonism and it is unlikely that it can be related to the trauma described.

On April 9, 1943, a medical board (Dr. C. E. Corlette, Dr. A. T. Nisbet, and Dr. Mackay) certified as follows:

> He has a festinant gait, a mask-like face, blurred speech, slow and deliberate movements and walks with

a stick. He had a fine hand tremor, but is not emotional. The pupils are equal and react to light and accommodation. The tongue, which is large and flabby, with some deep fissures, is not tender and is extruded in the midline. Both knee jerks are increased, the left more so than the right. Other tendon reflexes are normal. There is no Rombergism.

His wife said that, after the accident and the "stroke", he had gradually improved in all respects until he was walking with a stick; but in the last year he had become generally weaker and had by degrees lost control over his bladder and bowels. In the previous ten months he had been unable to speak properly except at certain times —for example, sometimes when explaining things mechanical to others. For six or seven months he had had generalized rigidity without tremor. He had never worked since the accident. The patient was a teetotaller, and smoked very little tobacco. There was no story of similar disease in his family. He had only one brother, who had died of burns, and one sister, who had been accidentally killed; neither of them had displayed during life any symptoms or signs of nervous disease. The patient's mother had died, at the age of eighty-eight years, after an abdominal operation. His father had succumbed to influenza and pneumonia at the age of eighty-seven years. All his grandparents had died of "old age", and none of these relatives had any brothers or sisters.

On examination of the patient on August 10, 1945, he was apyrexial, and, except for a blood pressure of 170 millimetres of mercury (maximum) and 115 millimetres (minimum), no abnormality was detected in the cardiovascular system. Respiration was noisy, the bubbling of saliva in the mouth and throat almost obscuring the breath sounds. The accessory respiratory muscles were in play, but there was little actual chest expansion. The percussion note was resonant all over the chest. Apart from tenseness of the abdominal wall musculature, no abnormality could be made out on abdominal examination. Examination of the nervous system showed the patient to be emotional and easily prone to tears, or more rarely to laughter. He could not speak intelligibly. Generalized rigidity was present, the hands being held partly flexed at the metacarpo-phalangeal joints. Some muscles showed flickering contractions, mainly in the legs, but not true fibrillary twitchings. No tremor was present. The cranial nerves were difficult to test, but appeared to be intact. Sensation was apparently normal, but slight generalized motor weakness was present. Except for absence of the left knee jerk, the tendon reflexes were more active than normal. The plantar reflexes were normal; the abdominal reflexes were doubtful.

On August 13 he had a sudden rise of temperature to 102° F. This was attributed to a urinary infection, the urine being found to contain pus. From time to time he passed urine or fæces in the bed. He was treated with potassium citrate and sulphanilamide, but administration of the latter drug was suspended on the following day owing to the poor urinary output. The temperature soon fell to about normal.

In the early morning of August 16 he could not be roused and his respirations were more stertorous than before. The limbs were still rigid, but all tendon reflexes were absent, and the plantar reflexes, though doubtful, appeared to be of the Babinski type, more noticeably on the left side. The right pupil was slightly smaller than the left, but both still reacted to light. This episode was considered to be the result of a cerebral thrombosis.

In the following two days he was again conscious and responding, the pupils now being equal and their reactions normal. However, on the morning of August 20 he was again difficult to rouse and looked very ill. At this stage it was just possible to elicit knee jerks. The temperature began to rise, continuing to do so until it reached 105·4° F. at 6 a.m. on August 21. His condition continued to deteriorate, and he died at 7 a.m. on the same day.

The clinical diagnosis was (i) Parkinson's syndrome, (ii) essential hypertension, (iii) cerebral thrombosis, (iv) cystitis.

Neuropathological Examination.

The brain and cord were received in 10% formalin solution and seemed well preserved. The whole brain weighed 1,391 grammes, the cerebral hemispheres accounting for 1,241 grammes, the cerebellum for 125 grammes, and the pons and medulla for the remaining 25 grammes. These figures give ratios to the whole brain weight of 89%, 9%, and 2% respectively, in lieu of the norms of 87%, 11% and 2%. These figures also pointed to a cerebellar involvement, a fact which was not at once appreciated. On naked eye examination but little was observed save that the pons, medulla and cord seemed on the small side.

Since the clinical signs and diagnosis pointed to the presence of lesions in the central nuclei and perhaps in the cord, these structures were specially examined in the general survey. However, the first five paraffin sections revealed extensive involvement of the central nuclei and olive cells, and something abnormal in the cerebellum. They also suggested that the neurones everywhere were especially susceptible to paraffin treatment, and so frozen sections were cut from every part where, among other structures, neurones had to be reported on. These sections were then stained by Mallory's toluidin blue (1%) in alcohol (20%) and mounted in distilled water with "Vaseline"-rimmed coverslips. Some of these sections kept permanently, and gave a useful picture of the neurones, the myelin, the adventitial cells and the vascular systems.

In common with Aring we found that while in paraffin sections peculiar Purkinje cells were seen, it was not till silver was applied that the wealth of torpedoes and swollen axis cylinders and collaterals showed up. This observer also gives a classification of cerebellar syndromes thus: (i) Friedreich's ataxia occurring in childhood; (ii) the subacute spino-cerebellar type of Greenfield, occurring in about the twenties and thirties, and characterized by cell and protein increases and gold sol reactions in the spinal fluid; (iii) the olivo-ponto-cerebellar types occurring at the age of about sixty years; and finally (iv) the chronic parenchymatous cortical cerebellar atrophy of Gordon Holmes, also occurring late in life, in which the intellectual faculties are well preserved. The slow, jerky speech, tremulous tongue and muscle infirmities of Aring's patient appeared to be due to incoordination rather than to actual weakness; in a way this case compares with ours, though it (Aring's case) represented a congenital deficiency.

The Pathological Findings in Brief.

Lesions affecting the myelin (and to a less extent the axis cylinders) were present in both ventral spino-cerebellar tracts in the upper cervical part of the cord and in the medulla, and also in the neurones of the olives and arcuate nuclei, the pontine nuclei, the *substantia nigra*, the optic thalami, the caudate nuclei, the putamen and the *globus pallidus* on either side. The myelin and axis cylinders of the external arcuate fibres, the interolivary, intraolivary and periolivary fibres, and some of the olivary-cerebellar fibres were also degenerated, as were also the transverse pontine and middle cerebellar peduncle fibres. Conspicuous glial reactions, both cellular and fibrous, were found in all affected areas and provided an outstanding feature, often obscuring the histology of the parts when not actually replacing them. In the cerebellum the myelinated white centres showed thinning of the myelin fibres, and to a less extent, of the axis cylinders. These parts commonly presented a convoluted or wavy arrangement, while innumerable extra nuclei and glial cells and fibres further complicated the picture. The Purkinje neurones were (i) entirely missing, or (ii) represented as mere squibs, or (iii) apparently unduly thinned in body but thickened in dendrite or plume and axis cylinder; some few were normal. The peripheral glia was grossly hypertrophied, the Burgmann less so, and at times the molecular layers were thinned while in the granule cells but little diminution had occurred. It was obvious that we had to deal with a case of Marie's ataxia or olivo-ponto-cerebellar atrophy, with those further involvements which vary from case to case.

Technique Employed.

Paraffin sections were prepared and the following stains were used: hæmotoxylin-eosin; Mallory's phosphotungstic

ILLUSTRATIONS TO THE ARTICLE BY PROFESSOR C. G. LAMBIE, DR. OLIVER LATHAM AND DR. G. L. McDONALD.

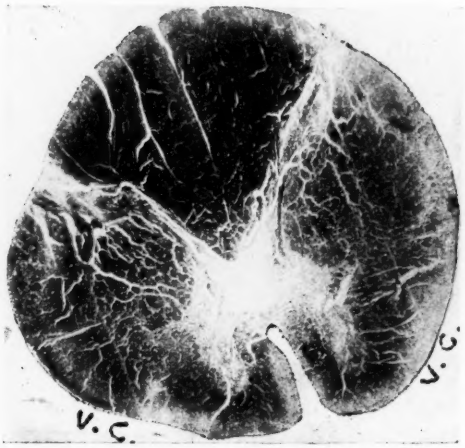


FIGURE I.

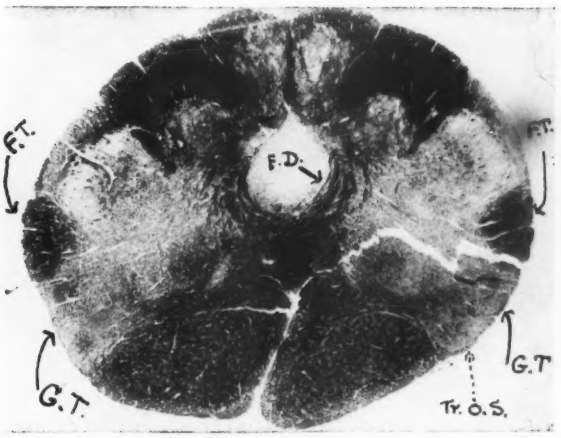
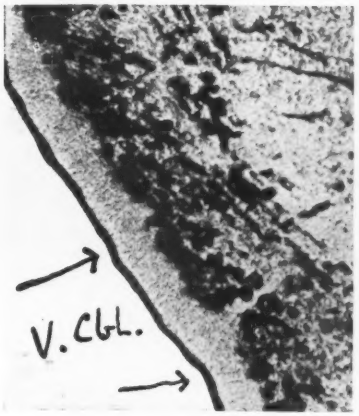


FIGURE II.

FIGURE III.



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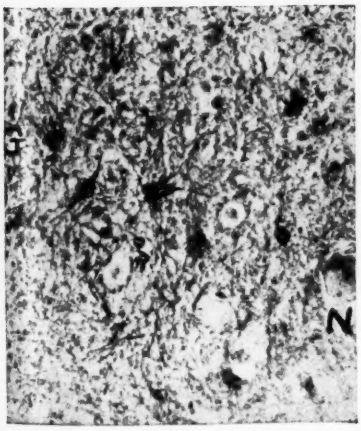

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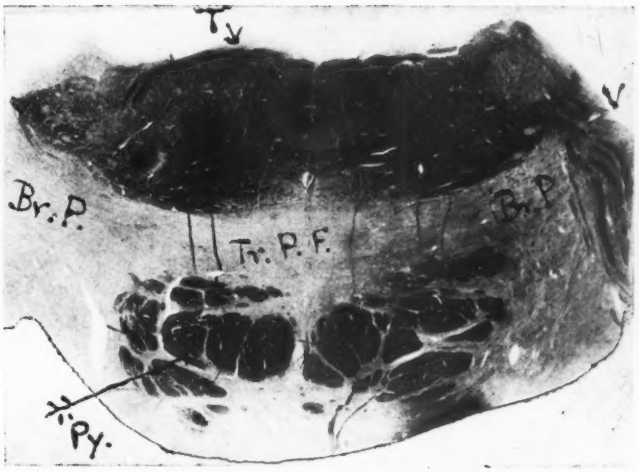

FIGURE VI.

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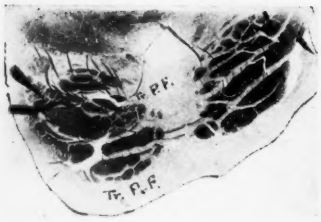

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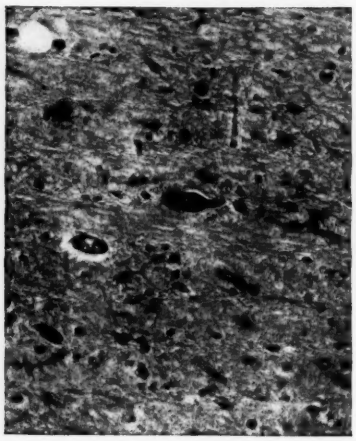
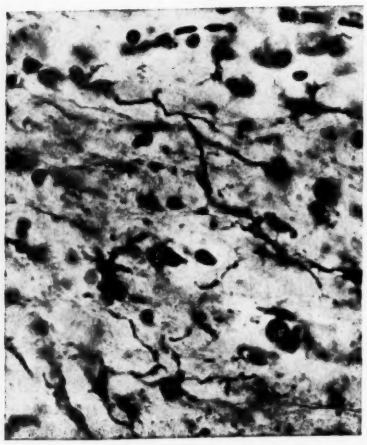


FIGURE VIII.



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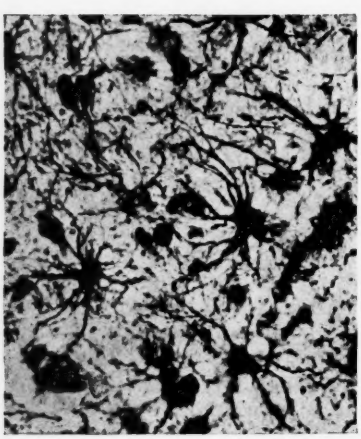
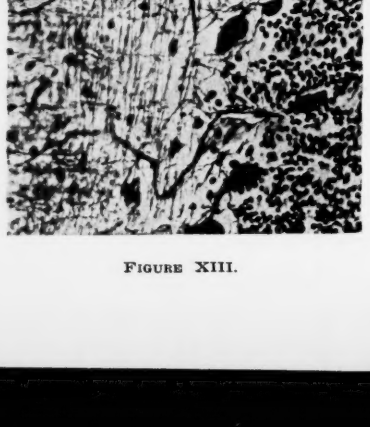


FIGURE X.

FIGURE XI.

FIGURE XII.



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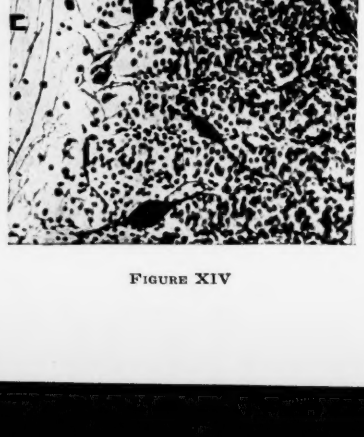

FIGURE XIV

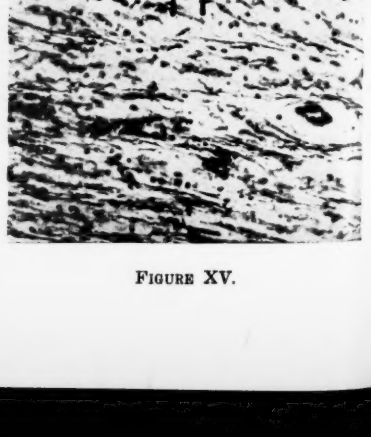

FIGURE XV.

hæmotoxylin stain and his triple stain; a four-colour method of L. H. Prince; iron-hæmotoxylin stain (for myelin) and Van Gieson's stain; Masson's trichrome stain; Nissl's stain for neurones; the Rogers-Foot and the Cobb-Pilcher techniques for silver sections.

Frozen section methods included (i) the Nissl method, (ii) the Weigert-Pal method; (iii) the Cajal-Ziehan gold-sublimate method for glia, (iv) the Cajal silver method for neurones, and (v) the Penfield-Cone and the Anderson-King techniques for microglia. Included also were von Braunmuhl's silver method for plaques and mesenchyme, Koneff's iron-hematoxylin-phospho-molybdic acid method, and Ford Robertson's modification of the Heller osmic acid method for myelin and his methyl violet glia stain.

Details of the Separate Lesions.

The Spinal Cord.—Many levels of the spinal cord from the lumbar to the cervical region were examined. The anterior horn cells showed considerable pigmentation, and a few exhibited axonal degeneration, while some were missing. The same may be recorded of the cells of Clarke's column; but it was considered likely that the great majority would be capable of functioning well. Greenfield, Noica *et alii*, have noted normal Clarke's column cells in extensive degeneration of the cerebellar tracts. In our case a definite degeneration of myelin fibres was present in the left ventral spino-cerebellar tract and somewhat less in the right tract, and the larger fibres were the most affected. These tracts were traced from the first cervical segment through many intermediate levels in the medulla till they took up their main position external and dorsal to the olives. The axis cylinders were less affected. It is a common sight, on occasions, to note definite paling of the olivo-spinal or Helwig's tracts. Both Noica *et alii* and Dejerine and Thomas considered that in their cases this paling constituted a lesion. While the area of whiteness seemed somewhat excessive and the glial framework rather obvious, it was not deemed worthy of further notice in our case.

The Medulla.—Examination of a Weigert-Pal preparation of the medulla about the centre of the olive revealed degeneration in the ventral spino-cerebellar tracts. In the atrophied olives commonly only 126 neurones were present, of which only 80 appeared normal. Normal figures range from 700 to 900 in comparative studies. In place of the nerve cells innumerable giant glial cells were present, dominating the fields. The periolivary, interolivary and intraolivary fibres were grossly degenerated, and the numbers of degenerated myelin fibres in the hila of the olives were so great that not only were these hila left white, but the accessory olives (usually in great part concealed by the crossing olivo-cerebellar fibres) here stood out in bold relief, bare and white. The accessory olives had also lost most of their nerve cells; but it must be added that at extreme caudal levels of the medulla, the olive neurones improved considerably, the ventro-median accessory olives to a less extent and the arcuate nuclei neurones hardly at all. The arcuate nuclei and fibres in nearly their entire extent had almost disappeared. The external arcuate fibres could be observed crossing the median raphe to travel on either side of the olives. Those best preserved on the ventral aspect appeared to lie dorsal to the arcuate nuclei. Few myelinated fibres appeared to arise in the arcuate nuclei, and there was a little thinning of the median raphe in its most ventral aspect. In contradistinction to the findings of Waggoner, Harris and other workers the *striæ acousticæ* and eighth nerves were not involved. The restiform bodies stained well, and Essick's bundles appeared normal, as did nearly all the fibres of Piccolomini up to the arcuate nuclei.

Pons, Lower and Upper Levels.—Weigert-Pal preparations readily showed the great degeneration of myelin fibres in the transverse pontine fibres and in the middle cerebellar peduncles, while, in contrast, the healthy fifth nerves and pyramids stood out black. In the pontine nuclei also was observed a grave reduction in their nerve cells, and many of those remaining presented either swollen states or pycnosis and axonal degeneration. The microglia was much activated, many rod cells being present, and all kinds of glial stains showed up the remarkable glial fibres and cell proliferation just here in both grey and white matter. In fact, some areas presented tangled masses of glia. In the dorsal parts of both medulla and pons a few neurones showed pigmentation and some loss; but compared with the ventral segments one might consider them normal. These pictures closely resemble those recorded by other observers of this syndrome.

The Brain Stem.—All parts of the brain stem appeared normal except the *substantia nigra*. This structure contained possibly less than half its normal number of neurones. It was affected by gliosis and neuronophagia. Many nerve cells here were deficient in, or were entirely without, their normal pigment, and the latter was to be found, not only scattered about (not in the same profusion as in *encephalitis lethargica*), but also in numbers of histiocytes. These conditions have also been noted by Waggoner and by Weil. In the hypothalamic region in places some cloudy swelling of the neurones was present, but most of these were healthy and little gliosis was observed. The superior cerebellar peduncles were normal.

Thalamus, Caudate Nucleus, Putamen and Globus Pallidus.—Examination of the thalami revealed much neuronophagia, and the nerve cells were heavily laden with pigment. Gliosis was observed in parts. In the caudate nuclei some neurone loss and degeneration were present. Far greater were the neurone degeneration and loss and the extent of the large cell gliosis in the putamen and *globus pallidus* on either side. Many of the larger and longer neurones escaped, though pigmentation was the rule, and in the *globus pallidus* many of the smaller neurones were represented by a nucleus and a tag or little bag of pigment. A fortunate silver impregnation of the large glial cells was obtained here, but actually other stains revealed equally large and numerous cells of this type in the pons, olives, arcuate nuclei and cerebellum. Examination of some of the vessels here and elsewhere, as in the cord, revealed that slight productive arteritis suggestive of moderate hypertension, and about the free borders and near the ependyma here and there many amyloid bodies were observed.

Cortex Cerebri.—The cerebral cortex was well preserved. The neurones were normal and there was but little gliosis save in the extreme frontal poles, where some subpial gliosis obtained, and elsewhere single large glial cells were observed here and there. In the vessels of the first layer some thickening was present, and in a few microscopic areas small groups of atretic nerve cells were encountered. No encephalitis was noted. Myelin stains showed that the *corona radiata* on both sides was well preserved.

The Cerebellum.—Besides many individual sections of the cerebellum, whole longitudinal giant paraffin sections were made—one through the vermis and the other a centimetre outside this, after the method of Tilney and Riley. Possibly the vermis was better preserved than the hemispheres; but without doubt the better preserved Purkinje cells were observed in the tonsils and in the most anterior part of the lobule. Elsewhere, apart from occasional better preserved folia (similar conditions prevailed throughout) many folia presented but two to five Purkinje cells in fair condition; other folia were without any or presented small squibs of nerve cells; or, on the other hand, they exhibited the type of degeneration called "cerebellopetal" wherein the Purkinje cell body is thinned and the axis cylinder and collaterals are thickened (even to the formation of torpedoes) and the dendrites, plumes or antlers are swollen and unduly conspicuous. In the better folia the baskets were fine and the horizontal fibres present in plenty; but for far the greater part the baskets (in contradistinction to the usual picture in the hereditary intracerebellar types) were only just visible and at times non-existent, and the horizontal fibres were thinned. In places the overlying pia was thickened, and doubtless the more degenerated folia lay here. The molecular glia from the pia was extremely hypertrophied and the Burgmann palisading obvious. The granular layer, if slightly thinned, was evenly so, and seemed to allow easier observance of the Golgi type II neurones. The myelin fibres of the white centres were

thinned and accompanied by such a degree of gliosis that the histological picture was obscured and altered, the fibres often taking on a wavy formation. This glial cell and fibre overgrowth was to some extent uneven and was greatest in the folia. The axis cylinders were not thinned to nearly the same extent as the myelin fibres, and the adventitial nuclei were much increased.

The Dentate Nuclei.—The dentate nuclei proverbially differ in size and preservation from case to case. Here they were on the small side and a certain number of the neurones showed degenerative phenomena; but even paraffin sections showed the great majority were well preserved, and it must be conceded that, as in the cases of Greenfield, Norce and Waggoner, these structures had practically escaped damage. Richter points out that they may be severely involved in arteriosclerosis. Some bands of myelin fibres near by were thinned.

Comparison of Cases.

Some twenty years ago Guillain, Mathieu and Bertrand described two cases of olivo-ponto-cerebellar degeneration with rigidity which had much in common with our case. Their cases were well illustrated and the pathology included lesions in areas such as the cord and central nuclei, outside the more usual cerebellar connexions in pons, medulla and cerebellum. Outstanding features were the destruction of olive cells and fibres, the arcuate system, the pontine nuclei and transverse fibres therein, the middle cerebellar peduncles, and (when they were not entirely destroyed) the damage to the Purkinje neurones. These features were common to both the cases of Guillain, Mathieu and Bertrand. In the Purkinje cells was seen that cerebello-petal type of degeneration wherein the cell body thins while the dendrites (or antlers) and the axis cylinders thicken (torpedoes), as do also the recurved collaterals. Baskets and horizontal fibres on the other hand were inconspicuous and not affected. The dentate nuclei and granular layers, as opposed to states observed in intracerebellar types, escaped. These observers also noted that when myelin fibres had degenerated the axis cylinders mostly escaped, and that widespread glial hypertrophy was pronounced. While the *substantia nigra*, red nuclei and central nuclei mostly escaped damage, in one of the cases certain bundles of myelinated fibres in connexion with the caudate and lenticular nuclei as well as in the crus (cerebro-pontine) were affected. Moreover, in one case paling was observed in the pyramidal and spino-cerebellar tracts, and in the other widespread degeneration of Clarke's column cells. In one case also myelin degenerations were found in the restiform bodies and in the medial raphe near by. The cerebral cortex and superior cerebellar peduncles escaped.

Comment.

A study of the literature dealing with cases of olivo-ponto-cerebellar atrophy seems to indicate that the lesions in the areas implied by the titles are the most constant and constitute a definite syndrome. Now these areas, which also include the arcuate system, are derived from the rhombic lip, and may possibly according to Essick be involved in some common developmental weakness or inherent incapacity to last. Therefore it is not surprising that these additional areas are at times affected. However, besides this one at times finds involvement of the spinal cord, the *substantia nigra*, Luy's bodies and the central nuclei—sometimes in respect of their neurones, sometimes in respect of their myelinated connexions and at other times in respect of both. Naturally, any additional areas involved in lesions will add their quota of clinical signs and present that confusion of symptoms which turns attention away from the more essential lesions in the cerebellar complex to signs more compatible with cord or central nuclei involvement.

Some embryological studies recently published in *Brain* by Dr. E. R. A. Cooper may perhaps throw some further light on the number of diverse structures in which lesions may be found in olivo-ponto-cerebellar degeneration. She has studied the development and differentiation of the alar and basal lamina of the mesencephalon and calls attention to the splitting up and separation of these cell layers by descending cerebral tracts, *et cetera*. In time there are developed from these nuclear columns caudate nucleus, putamen, *globus pallidus*, red nucleus, *substantia nigra*, pontine nuclei, bulbar olives and arcuate nuclei, any or all of which structures may be involved in so-called cerebellar syndromes.

Summary.

1. A case of Marie's ataxia or olivo-ponto-cerebellar degeneration has been presented and the findings have been compared with those found elsewhere in similar cases.

2. Additional lesions were found in the *substantia nigra*, cord and central nuclei.

3. An interesting feature was that this systemic disease of slow onset was first noticed soon after the patient had suffered a body injury by being knocked down by a motor lorry and having his leg broken.

4. The diagnosis of Parkinsonism was made in two independent clinics. The main incidence of the lesions fell on the palæocerebellum and its afferent tracts.

It is difficult to assess the relative importance of the lesions here and in the caudate nucleus, putamen, *globus pallidus* and *substantia nigra* in the production of the clinical signs; but attention is drawn to the possible significance of the lesions in the posterior part of the palæocerebellum.

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Legends to Illustrations.

FIGURE I.—First cervical level. Note the partial demyelination of the ventro-cerebellar tracts (V.C.). These lesions have been traced up through many levels in the medulla. Silver stains show that many axis cylinders escape. (Weigert-Pal stain; × 8.)

FIGURE II.—Cross section of the medulla at the caudal level of the fillet decussation. Demyelination may be seen in both Gower's ventral spino-cerebellar tracts (G.T.), while the dorsal cerebellar tracts of Flechsig (F.T.) conspicuously escape. Some paling may also be seen in the olivary spinal tracts (O.S.). The fillet decussations (F.D.) are well stained. (Weigert-Pal stain; × 6.)

FIGURE III.—Transverse section of medulla about the middle of the olive. The myelin stain enables one to see the normal myelin staining black, while the olives are pale and their intraolivary, interolivary and periolivary fibres are grossly affected. Thus the hyla are pale and the accessory olives stand out conspicuously white from degeneration of the olivary-cerebellar fibres (A.O.) which commonly pass through them. The neurones of the ventral arcuate nuclei (N.A.) have practically disappeared, and thus but few fibres are relayed to help form the external arcuate fibres (F.A.E.), and but few myelin fibres pass round the exterior of the olives (P.O.). Posterior to the olives on either side, the ventral spino-cerebellar tracts (V.C.) are obviously pale. The restiform bodies escape damage, and the pyramids and medial raphe and *fasciculus solitarius* on either side are also normal.

FIGURE IV.—Close-up view of one of the ventral spino-cerebellar tracts (the left) taken just behind the angle made by the bulge of the olive (V.Cbl.). (Weigert-Pal stain; × 60.)

FIGURE V.—Portion of the folia of an olive section showing but one normal neurone (N) and innumerable large neuroglial cells and fibres (G). (Mallory's phospho-tungstic hæmatoxylin stain; × 450.)

FIGURE VI.—Cross section of the pons about the fifth cranial nerve (V), showing the gross degeneration of the transverse pontine fibres (Tr.P.F.) and the *brachium pontis* (Br.P.), while the pyramids (Py.) and fifth nerve (V) and tectum (T) quite escape and stain black. (Weigert-Pal stain; × 4. Where white portions of sections shade into the white of the background, these lines of poor demarcation are etched in.)

FIGURE VII.—A section of the pons taken at a higher level (under the aqueduct) corroborates the last picture. The transverse pontine fibres (Tr.P.F.) are still deeply degenerated, while the pyramids (stained deep black) escape. (Weigert-Pal stain; × 2.) The top of this section (not included in the field) shows that the superior cerebellar peduncles as a whole stain well.

FIGURE VIII.—Section through part of the pontine nuclei. The loss of pontine nuclei neurones in this section is shown

by the presence of but one or two in the field, the other nuclei being those of various numerous and hypertrophied glial cells. (Special four colour stain; × 450.)

FIGURE IX.—Rod cells and other forms of microglial reaction among the pontine nuclei are brought out as deep black wavy lines by Penfield-Cone's silver stain. (× 450.)

FIGURE X.—This section from the *globus pallidus* (Penfield-Cone stain over reduced) reveals the giant glial cell reaction, presumably a type of replacement glia, for many neurones here are degenerated. Many other glial stains corroborate these pictures, and in fact this picture would do for parts of the caudate nuclei, putamen, pons, olives and accurate nuclei, especially the last-mentioned, in which there were gross losses of neurones and glial overgrowth. (× 450.)

FIGURE XI.—This section stained by von Braunmuhl's silver technique reveals the great glial fibre overgrowth in the cerebellar molecular layer. It also shows the persistence of the horizontal fibres, the inconspicuousness of the baskets and the absence of Purkinje neurones. (× 200.)

FIGURE XII.—Cerebellar cortex. Four Purkinje neurones, which looked strange by hæmatoxylin and eosin staining, by the same silver stain are seen to be thin in outline, with thickened antlers or dendrites (A). The one on the extreme right shows a thickened axis cylinder running down in the granular layer, which seems fairly normal. (× 200.)

FIGURE XIII.—The same stain shows three diseased Purkinje cells and no less than five axis cylinder swellings (torpedoes) seen as dense black oval bodies in the granular layer, the dotted part below. (× 200.)

FIGURE XIV.—This partly oblique section of part of a cerebellar folia shows torpedoes, swollen axis cylinders and recurved collaterals. Besides these, horizontal fibres (H) are seen as well as the white centre of axis cylinders which stain fairly well (right hand top corner). However, many of these black fibres are glial. The granule layers are fair. (Von Braunmuhl stain; × 200.)

FIGURE XV.—Portion of the white centre of the cerebellum stained by the Weigert-Pal method shows definite thinning of the myelinated fibres (M). (× 400.)

Bibliography.

C. D. Aring: "Cerebellar Syndrome in an Adult with Malformation of the Brain Stem and Cerebellum (Arnold Chiari Syndrome), with a Note on the Formation of Torpedoes", *The Journal of Neurology and Psychiatry*, Volume I (New Series), 1938, page 100.

S. P. Bakker: *"Atrophia olivo-ponto-cerebellaris"*, *Zeitschrift für die gesamte Neurologie und Psychiatrie*, Volume LXXXIX, 1924, page 213.

L. Barker: "A Description of the Brains and Spinal Cords of two Brothers Dead of Hereditary Ataxia: Cases XVIII and XX of the Series of the Family Described by Sanger Brown, with a Clinical Introduction by Sanger Brown", *Decennial Publications of the University of Chicago*, Volume X, 1903, page 349.

R. Bing: *"Die Abnützung des Rückenmarkes (Friedreichsche Krankheit und Verwandtes)"*, *Deutsche Zeitschrift für klinische Medizin*, Volume LXXXIII, 1905, page 71.

Sanger Brown: "On Hereditary Ataxia, with a Series of Twenty-one Cases", *Brain*, Volume XV, 1892, page 250.

A. W. Campbell, W. F. Lichfield and O. Latham: "A Clinical and Anatomical Report of a Case of Friedreich's Ataxia", THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, 1917, page 136.

Combette: *Journal de physiologie de Magendie*, 1831; quoted by H. Royet and J. Collet, *loco citato*.

E. R. A. Cooper: "Development of the Substantia Nigra, Red Nucleus and Corpus Striatum", *Brain*, Volume LXIX, Part 1, 1946, page 22.

J. Cruveilhier: *"Anatomie pathologique"*, 1835-1842, Volume II, Book 32, Plate II.

L. Dejerine and A. Thomas: *"L'atrophie olivo-ponto-cérébelleuse"*, *Nouvelle iconographie de la Salpêtrière*, Volume XIII, 1900, page 330.

G. M. Duchenne: *"Ataxie locomotrice progressive"*, *Archives générales de médecine*, December, 1858, and January, February, and April, 1859.

E. Larus and H. Okkels: *"Les glandes endocrines et le cerveau dans la vieillesse"*, *Annales d'anatomie pathologique*, Volume XIII, 1936, page 557.

C. Essick: "The Corpus Ponto-Bulbare. A Hitherto Undescribed Nuclear Mass in the Human Brain", *American Journal of Anatomy*, Volume VII, 1907, page 119; "The Development of the Nuclei Pontis; the Nucleus Arcuatus in Man", *American Journal of Anatomy*, Volume XIII, 1912, page 55.

D. Fraser: "Defect of the Cerebellum Occurring in a Brother and Sister", *Glasgow Medical Journal*, Volume XIII, 1880, page 199.

S. Freud: *Neurologische Centralblatt*, Volume XII, 1893; quoted by P. Marie: *"Über familiäre Formen von cerebralen Diplegien"*.

N. Friedreich: *"Über degenerative Atrophie der spinaler Hinterstränge"*, *Archiv für pathologische Anatomie*, Volume XXVI, 1863, page 391; *"Über degenerative Atrophie der spinaler Hinterstränge"*, *Archiv für pathologische Anatomie*, Volume XXVII, 1863, page 1; *"Über Ataxie mit besonderer Berücksichtigung der herediterären Formen"*, Volume LXVIII, 1876, page 145; *"Über Ataxie mit besonderer Berücksichtigung der hereditären Formen"*, Volume LXX, 1877, page 140.

J. S. Greenfield: "Subacute Spino-Cerebellar Degeneration Occurring in Elderly People", Volume XLVII, 1934, page 161.

G. Guillain, P. Mathieu and L. Bertrand: *"Étude anatomo-clinique sur deux cas d'atrophie olivo-ponto-cérébelleuse avec rigidité"*, *Annales de médecine*, Volume XX, 1926, page 417.

B. Hall, K. B. Noad and O. Latham: "Familial Cortical Cerebellar Atrophy", THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, 1945, page 101; "Familial Cortical Cerebellar Atrophy", *Brain*, Volume LXIV, 1941, page 178.

G. B. Hassin and T. H. Harris: "Olivo-Ponto-Cerebellar Atrophy", *Archives of Neurology and Psychiatry*, Volume XXXV, 1936, page 43.

G. B. Hassin: "Marie's Ataxia (Olivo-Ponto-Cerebellar Atrophy)", *Archives of Neurology and Psychiatry*, Volume XXXVII, 1937, page 1371.

G. Holmes: "A Form of Familial Degeneration of the Cerebellum", *Brain*, Volume XXX, 1907, page 466; "An Attempt to Classify Cerebellar Disease, with a Note on Marie's Cerebellar Ataxia", *Brain*, Volume XXX, 1907, page 548.

R. Hunt: "Causation of Paralysis Agitans", *Archives of Neurology and Psychiatry*, Volume XXX, 1933, page 1349.

J. R. M. Innes: "'Swayback': Congenital Demyelinating Disease of Lambs with Affinities to Schilder's Encephalitis", *Proceedings of the Royal Society of Medicine*, Volume XXIX, 1936, page 406; abstracted in *Archives of Neurology and Psychiatry*, Volume XXXIX, 1938, page 380.

J. Jansen: "Experimental Studies on Intrinsic Fibers of Cerebellum; Arcuate Fibers", *The Journal of Comparative Neurology*, Volume LVII, 1933, page 369; abstracted in *Archives of Neurology and Psychiatry*, Volume XXXV, 1936, page 151.

B. Kecht and E. Pollak: *"Die diffuse Kleinhirnsclerose"*, *Jahrbuch für Psychiatrie und Neurologie*, Volume LIII, 1936, page 45; abstracted in *Archives of Neurology and Psychiatry*, Volume XXXVIII, 1937, page 622.

W. Keiller: "Four Cases of Olivo-Ponto-Cerebellar Atrophy Giving a History of Heredity, with Three Autopsies", *Southern Medical Journal*, Volume XIX, 1926, page 518.

J. W. Kernahan: "Cerebellar Atrophy", *Archives of Neurology and Psychiatry*, Volume XXXIII, 1935, page 968.

O. J. Klippel and G. Durante: *"Contribution à l'étude des affections nerveuses familiales héréditaires"*, *Revue de médecine*, Volume XII, 1892, page 745.

O. Larsell: "The Cerebellum—a Review and an Interpretation", *Archives of Neurology and Psychiatry*, Volume XXXVIII, 1937, page 580.

R. Ley: *"Forme atypique d'atrophie cérébelleuse ayant évolué en syndrome rigide"*, *Archives internationales de médecine expérimentale*, Volume I, 1924-1925, page 277.

B. W. Lichenstein: "Cerebellar Atrophy", *The Journal of Neuropathology and Experimental Neurology*, Volumes III-IV, 1944-1945, page 379.

G. Moruzzi: *"Recherche sulla fisiologia del paleocerebellum. I. Riflessi labirintici e cervicali, paleocerebellum e tono posturale"*, *Archivio di fisiologia*, Volume XXXVI, 1936, page 57; *"II. Riflessi proprioceptivi somatici, paleocerebellum e tono posturale"*, *ibidem*, Volume XXXVI, 1936, page 337; *"III. Sulla natura e sul meccanismo dell' inversione dell' inhizione paleocerebellare"*, *ibidem*, Volume XXXVI, 1936, page 408.

F. Raymond: *"Maladie de Friedreich et l'hérédo-ataxie cérébelleuse"*, *Nouvelle iconographie de la Salpêtrière*, Volume XVIII, 1905, page 121.

G. E. Rennie: "A Case of Friedreich's Hereditary Ataxia with Necropsy", *British Medical Journal*, Volume II, 1899, page 129.

R. Richter: "Clinico-pathologic Study of Parenchymatous Cortical Cerebellar Atrophy; Report of a Familial Case", *The Journal of Nervous and Mental Diseases*, Volume XCI, January, 1940, page 37; abstracted in *Archives of Neurology and Psychiatry*, Volume XLIV, 1940, page 900.

H. Royet and J. Collet: *"Sur une lésion systematisée du cervelet et ses dépendances bulbo-protubérantielles"*, *Archives de neurologie*, Volume XXVI, 1893, page 353.

F. Schultze: *"Über einen Fall von Kleinhirnschwund mit Degenerationen im verlängerten Marke und Rückenmarke (warscheinlich im Folge von Alkoholismus)"*, *Virchows Archiv für pathologische Anatomie*, Volume CVIII, 1887, page 331.

O. G. L. Seeligmüller: *"Hereditäre Ataxie mit Nystagmus"*, *Archiv für Psychiatrie und Nervenkrankheiten*, Volume X, 1879, page 222.

W. Seiffer: *"Über die Friedreische Krankheit und ihre Trennung in eine spinale und cerebellare Form"*, *Charité Annalen*, Volume XXVI, 1902, page 83.

E. B. Stanley: *Medico-chirurgical Transactions*, Volume II, Series V, 1840, page 31.

F. Tilney and H. A. Riley: "The Form and Functions of the Central Nervous System", 1921.

R. W. Waggoner *et alii*: "Hereditary Cerebellar Ataxia", *Archives of Neurology and Psychiatry*, Volume XXXIX, 1937, page 570.

A. Weil: "Text-book of Neuropathology", Second Edition, 1945.

O. Wennicke: *"Über die hereditäre Ataxie Friedreichs und die hérédo-ataxie cérébelleuse s. Maries im Anschluss an 2 in der Kaiserlichen Nervenpoliklinic zu Breslau beobachtete Fälle"*, Inaugural Dissertation, Breslau, 1903.

C. Winkler: "Case of Olivo-Ponto-Cerebellar Atrophy and our Conception of Neo- and Palæo-cerebellum", *Schweizerische Archiv für Neurologie und Psychiatrie*, Volume XIII, 1923, page 684.

P. Lowe: *"L'atrophie olivo-ponto-cérébelleuse (type Dejerine-Thomas)"*, 1903.

P. Londe: *"L'hérédo-ataxie cérébelleuse"*, *La presse médicale*, Volume III, 1895, page 385.

P. Marie: *"Sur l'hérédo-ataxie cérébelleuse"*, *La semaine médicale*, Volume XIII, 1893, page 444.

P. Menzel: *"Beitrag zur Kenntnis der hereditärer Ataxie und Kleinhirnatrophie", Archiv für Psychiatrie,* Volume XXXII, 1891, page 160.

A. Meyer: "The Morbid Anatomy of a Case of Hereditary Ataxia", *Brain,* Volume XX, 1897, page 276.

G. Mingazzini: *"Klinischer und pathologisch-anatomischer Beitrag zum Studium der Kleinhirnatrophie der Menschen", Monatsschrift für Psychiatrie und Neurologie,* Volume XVIII, 1905, page 261; *"Weitere Beiträge zum Studium der Friedreich-schen Krankheit", Archiv für Psychiatrie und Nervenkrank-heiten,* Volume XLII, 1906, page 917.

G. Mingazzini and G. Perusini: "Two Cases of Familial Heredo-spinal Atrophy", *The Journal of Mental Pathology,* Volume VI, 1904-5, page 14.

S. J. Minogue and O. Latham: "Cerebellar Degeneration with Epilepsy". THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, 1945, page 430.

M. Nonne: *"Über eine eigentümliche familiäre Erkrankungs-form des Centralnervensystems", Archiv für Psychiatrie,* Volume XXII, 1891, page 283; *"Ein weiterer anatomischer Befund bei einem Fall von familiärer Klenhirnataxie", Archiv für Psychiatrie,* Volume XXXIX, 1905, page 225.

D. Noica, J. Nicolesco and T. Hornet: *"A propos de l'atrophic olivo-cérébelleuse", Encéphale,* Volume XXXI, 1936, page 372; abstracted in *Archives of Neurology and Psychiatry,* Volume XXXVIII, 1937, page 1305.

L. Ollivier: *"Traité des maladies de la moelle épinière",* Third Edition, Volume II.

J. M. Pierret: *"Note sur un cas d'atrophie périphérique du cervelet, avec lésion concomitante des olives bulbaires", Archives de physiologie,* 1872; quoted by H. Royet and J. Collet, *loco citato.*

N. Zande: *"Le rôle des olives bulbaires", Encéphale,* Volume XXXI, 1936, page 270; abstracted in *Archives of Neurology and Psychiatry,* Volume XXXVIII, 1937, page 390.

Reviews.

ANATOMY FOR PHYSIOTHERAPISTS.

EWART'S "Guide"[1] has now attained its sixth edition and evidently fulfils a steady demand. In this edition the Birmingham Revision nomenclature is adopted. Any remarks on a book of this kind must take into account the fact that it is designed primarily for physiotherapists who in England do not, as in Australia, engage in actual dissection. Such restriction limits the scope of the work so that it becomes little more than an illustrated catalogue of bones, muscles, joints, vessels, nerves and viscera. And the illustrations are not, in fact, particularly good. For example, such important things as the interossei muscles and the reciprocal insertion of the superficial and deep long flexors, which are only briefly mentioned in the text, are not illustrated at all. Also, in view of the growing importance of ante-natal and post-natal exercises in the practice of physiotherapy, much more attention should have been given to the details of the anatomy of the female pelvis; but the "Guide" is almost asexual. Unless supplemented by ample access to dissected specimens this book is simply an examination passing aid, to be learnt parrot fashion. The suspicion that this, rather than an effort to impart real understanding of human anatomy, is its main purpose, is strengthened by the fact that a number of sample examination papers is included at the end.

DYNAMIC BIOCHEMISTRY.

BALDWIN'S "Dynamic Aspects of Biochemistry" is probably the forerunner of a new type of textbook of biochemistry.[2] From it descriptive matter has been entirely excluded. Attention is focused on the metabolic changes which compounds of biochemical interest undergo in the living body. Knowledge of the properties of the compounds which he studies is, of course, essential to the biochemist, but it is not his main interest, as it is of the organic chemist.

The present textbook has been designed primarily for students of science taking biochemistry as a major subject. The author does not intend it to supplant the type of text at present used by medical and other students whose interests are predominantly biological. Without radical alterations to the curricula of such students their biochemical texts must continue to embody a good deal of descriptive material. Baldwin's book will provide a valuable extension to the reading of these students from the third year onwards. It will also be of great interest to the graduate who wishes to maintain his interest in the chemical processes underlying the principal metabolic changes of the body and to bring his knowledge up to date.

The book has been written in a manner which stimulates thought. A certain amount of speculative material has admittedly been included to preserve continuity, and some of this may rapidly become obsolete. The main outlines of the principal metabolic events of the body are, however, now apparent, and our view of them is not likely to alter essentially during the next few years. The clarity of the book is greatly helped by the numerous diagrammatic schemata of metabolic cycles. The author feels it necessary to apologize for the unconventionality of some of these presentations, but the average reader will be very appreciative of them.

The book is divided into two parts. In Part I (the first third) the general principles of enzyme action are clearly presented, and the various classes of enzyme systems are discussed. Part II is devoted to metabolism, including digestion. The interrelations of the more important metabolites are discussed, as well as the changes which the proteins, carbohydrates and fats themselves undergo in the body. Where the accompanying energy changes are of importance, as in the complex cycle of events involved in the contraction of muscle, they too are discussed.

There is no discussion of the inorganic *milieu* in which all the changes of the organic metabolites take place. This is a common lack in textbooks of biochemistry. Perhaps in this instance the author feels that our knowledge of this aspect of the subject has not yet emerged sufficiently from the descriptive stage.

A small but well selected list of references and a very comprehensive index complete this excellent book.

SURGICAL PATHOLOGY.

THERE are a few books—very few—which the practising surgeon must have. William Boyd's "Surgical Pathology" is one of these. A sixth edition has now been published.[1] Numerous additions have been made, but the purpose of the book remains unchanged, namely, to present those aspects of pathology which will be useful to the surgeon.

The book is now so familiar to pathologists and surgeons that only the changes in this edition need be mentioned. An entirely new section has been added dealing with the pathology and pathological physiology of congenital heart disease. Other new material includes tumours of the larynx, pinealoma, Bittner's milk factor in relation to breast carcinoma, the vaginal smear in the diagnosis of carcinoma of the cervix, fibrous dysplasia of bone, the inflammatory nodules of muscle in chronic arthritis, and some of the recent work by Copeman and Ackerman on fibrositis of the back.

The book is well produced, and is a pleasure to read and handle. The references at the end of each chapter need more careful revision. A full index is provided.

ANATOMICAL PLATES.

J. J. TEKLENBURG has produced a small volume of anatomical plates which are chiefly intended for the instruction of first-aid students and student nurses.[2] It is hoped by the author that the book may be of interest also to members of the general public.

The plates, fifteen of which are in colour, show diagrams of the various systems of the body with accompanying legends. There is no text and no index.

The book should prove of value for those for whom it is intended, especially if it is used in classes. We would suggest that the atlas would be more useful if more "regional" anatomy was included.

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[1] "A Guide to Anatomy: For Students of Physiotherapy and Electro-Therapy, etc.", by E. D. Ewart; Sixth Edition; 1947. London: H. K. Lewis and Company, Limited. 8¼" × 5¼", pp. 330, with many illustrations, some of them coloured. Price: 25s.

[2] "Dynamic Aspects of Biochemistry", by Ernest Baldwin, B.A., Ph.D.; 1947. Cambridge: The University Press. 8½" × 5½", pp. 470. Price: 21s.

[1] "Surgical Pathology", by William Boyd, M.D., Dip.Psychiat., M.R.C.P. (Edinburgh), F.R.C.P. (London), LL.D. (Sask.), M.D. (Oslo), F.R.S.C.; Sixth Edition; 1947. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9½" × 6¼", pp. 858, with many illustrations, some of them coloured. Price: 70s.

[2] "Handbook of Elementary Anatomy: Specially Prepared for First Aid Students, Student Nurses, et Cetera", by John J. Teklenburg; 1947. London: H. K. Lewis and Company, Limited. 9½" × 6", pp. 36, with 16 coloured illustrations. Price: 5s. 6d.

The Medical Journal of Australia

SATURDAY, NOVEMBER 22, 1947.

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RADIOACTIVE ISOTOPES AND THEIR USES.

As radioactive isotopes become more and more widely used in clinical medicine and in medical research, the references to them in medical literature naturally become more numerous. What was at first almost an esoteric subject in medicine has become comparatively well known. It is necessary with this, as with other obscure subjects, that fact should always be sharply distinguished from conjecture, that what is known to occur as a result of properly controlled observation and experiment should not be confused with what may be assumed in the light of insufficient evidence. Accuracy in the mind of the clinician is all the more necessary because of the way in which the members of the community are provided in popular magazines of a certain type with accounts of medical writings from which unjustifiable conclusions may be drawn. On two previous occasions the subject of isotopes has been mentioned at some length in these columns. On September 8, 1945, the therapeutic use of radioactive phosphorus was discussed in the light of several contributions to the literature; on August 10, 1946, the subject dealt with was radioactive iodine therapy in hyperthyreoidism. In 1945 J. G. Hamilton was quoted as stating that almost all of the elements and compounds present in biological systems could be "tagged" with the aid of artificial radio-elements and their course in living structure directly studied. Hamilton also stated (he wrote in 1942) that radioactive isotopes of twenty-one elements had been used in various fields of investigation and that practically all the biological sciences had been included. J. H. Lawrence, writing recently on the use of isotopes in medical research,[1] reminds us that with methods now available radioactive forms of nearly all the ninety-six elements known in the periodic system can be made artificially. In the circumstances it will probably be useful to draw attention to the subject once more and to refer to one or two recent contributions to the literature. If a picture of use to those unfamiliar with the subject is to be produced, elementary facts may have to be stated and work previously mentioned referred to once more.

In 1945 we referred to the discovery of artificial radioactivity by Curie and Joliot in 1934 as having opened up a new field of study. J. Gross and C. P. Leblond, of the McGill University, Montreal, in a review of histological localization of radioactive elements[1], point out that the ability of radioactive rays to affect photographic emulsions was discovered before radioactivity itself was known to exist. H. Besquerel suspected the fact in 1895 when he found that a fragment of uranium ore left next to a photographic plate produced fogging of the plate. Having made this chance observation, he placed a layer of crystalline uranium sulphate over a photographic plate wrapped in black paper. On development the plate showed the silhouette of the crystals. From this first "autograph" he concluded that uranium produced mysterious rays which acted on photographic emulsions. The same type of technique is used today in the detection of radioactive substances introduced into the body—the tissue under investigation is placed on a photographic plate. The image obtained is known as the "histoautoradiograph", the "radioautograph", or the "autograph". The photographic emulsion used on a plate or film is a suspension of a silver salt, generally silver bromide, in a gelatin matrix. The rays given off by radioactive elements have an effect on the photographic emulsion similar to that of light. The effect, however, differs for each type of radiation, according to whether it consists of α, β or γ rays. The α particles are the most effective in "autography", the β particles are somewhat less, and the γ radiation is still less effective. When the autograph of an animal's tissues is to be obtained, the material, the isotope under investigation, is injected into the animal. After a sufficient period of time to allow the radioactive substance to be distributed in the body, the animal is sacrificed and tissues are excised for examination. The tissues are fixed, embedded in paraffin and sectioned. The sections are mounted on microscope slides and dried. The slides are then placed in contact with a photographic emulsion on a plate or film. The plate or film is developed after an exposure the length of which depends on the "half-life" of the isotope used. The half-life of a radioactive isotope is, in the words of Gross and Leblond, the time required for half the initial stock of atoms to decay. The half-life varies with the isotope used. Lawrence has an interesting table in which the half-life of the several isotopes is set out. To show the tremendous variation two radioactive isotopes of carbon may be quoted, C^{11} and C^{14}; the former has a half-life of about twenty-one minutes, the latter a half-life of about 6000 years. Gross and Leblond, who, as already stated, are concerned in their review only with the histological localization of radioactive elements, discuss the isotopes that have been studied so far—polonium, lead, phosphorus, calcium, strontium and iodine. The list, they believe, will before long be considerably extended. But the histological localization of radioactive elements is only one of the practical uses to which isotopes can be put. At this stage we may do well to recall the way in which isotopes may be produced; this is described by Lawrence. The isotope

[1] *The Journal of the American Medical Association*, May 17, 1947.

[1] *The Canadian Medical Association Journal*, August, 1947.

of an element is a form of an element which has an atomic weight different from that of the usual form. All isotopes are not radioactive. The most efficient ways of producing radioactive isotopes involves the use of the cyclotron or the uranium pile. Lawrence explains that in the cyclotron "positively charged nuclear particles are accelerated". He quotes as an example the fact that if radioactive iodine is to be made, a target of the element tellurium (which is next to iodine in the periodic table) may be bombarded with deuterons. The result is that some of the tellurium atoms are transformed into I^{131}, a radioactive isotope which emits β and γ rays. The uranium pile is in many cases able to make larger quantities of isotope than the cyclotron. For example, ordinary N^{14} can be converted into long-lived radioactive C^{14}. The target is nitrogen in the form of some compound of nitrogen such as ammonium nitrate. The bombarding bullet is a slow neutron, and a pile is the source *par excellence* for slow neutrons. The nitrogen nucleus gains a neutron, but loses a proton, and thus is transformed into carbon of atomic weight 14. At this spot one may perhaps pause to marvel at this modern alchemy and to wonder whether man will ever realize the dream of the ancient alchemists who sought to turn baser metals into gold. But this is idle speculation.

There are two uses to which radioactive isotopes may be put. The first is the therapeutic use which was mentioned in our previous discussions of 1945 and 1946. The other is their use as "tracers" in research and metabolic studies. In the latter the doses used are so small that no biological effect is produced; in therapeutic work the doses are of necessity much larger. In research several techniques may be employed. The "autographic" method has already been mentioned. The second and, as Lawrence tells us, the most widely used, technique is the *in vitro* method. In this, samples of material such as blood, spinal fluid, urine, stools or tissues, taken at various periods of time after administration of the radioactive material, are weighed, ashed and measured for activity. The third technique is the *in vivo* method and in this an instrument known as the counter counts the number of rays emitted per unit of time. The counter tube is passed over the surface of an animal that has received a radioactive compound and an increase in the counting rate is noted on an approach to a particular tissue in which the compound has become localized. This technique has been used to measure the time required for the blood in a normal person to reach the heart from the arm after the injection into the antecubital vein of a small amount of radioactive sodium chloride in isotonic solution. This technique has also been used in studies of thyreoid metabolism, in association with skin temperature measurements in studies of vascular disease, in the estimation of the adequacy of the circulation and in studies in the vagina and rectum. When radioactive isotopes are injected into the body they show what is known as selective localization. For example, the thyreoid gland absorbs iodine and provides the best example of selective localization. The therapeutic use of isotopes is based on selective localization, and it is in the therapeutic aspect, in which an attempt is made to substitute isotopes as a source of irradiation for X rays and radium, that the clinician is chiefly interested.

In regard to treatment with radioactive isotopes, we would refer readers to our previous discussions. It will be remembered that the work on radioactive iodine and hyperthyreoidism was encouraging, but that much more investigation was thought to be necessary before the place of this isotope treatment in thyreoid therapy could be determined. Lawrence refers to a report by Seidlin, Marinelli and Oshry of a cure effected by radioactive iodine in a case of carcinoma of the thyreoid. In this instance metastasis to bone had occurred. The patient was very ill and emaciated, but after three years was apparently well and was enjoying normal life. The significance of this one case lies probably in the demonstration that it gives of the concentration of radioactive iodine by thyreoid tissue, rather than in any general efficacy of the method. Lawrence observes that in the evaluation of any new form of therapy the questions asked are: "Does the treatment cure the disease?" and "Is comfortable life prolonged?" He makes this observation in his remarks on the use of radioactive phosphorus in leuchæmia. He points out that in all reports the belief has been expressed that this form of therapy is as good as, and possibly better than, X radiation, but that the two questions have not been answered. Bearing this in mind, we may now turn to a report that comes from the Department of Medicine in Ohio State University; the authors are C. A. Doan, B. K. Wiseman, Claude Starr-Wright, J. A. Geyer, W. Myers and J. W. Myers.[1] They report experience with radioactive phosphorus, P^{32}, extending over a six year period, and they deal all together with 100 cases. In this group were included cases of *polycythæmia vera*, cases of leuchæmia of various kinds, Hodgkin's syndrome and some malignant conditions. These authors present certain interesting conclusions. First of all radioactive phosphorus has in their experience been of most value in *polycythæmia rubra vera*. It is also a valuable adjunct to other therapy in certain of the more chronic leuchæmic states, particularly in those cases in which there is intolerance of, or resistance to, X radiation. The splenomegaly of chronic myeloid leuchæmia was often found to be more resistant to P^{32} than to deep X-ray therapy. P^{32} appeared "all too frequently" to accentuate the clinical acuteness of acute leuchæmia and was never found to be permanently beneficial. P^{32} failed to control Hodgkin's syndrome and was found to threaten the integrity of the marrow unless great care and discretion were shown in the doses used. The pain associated with metastatic malignant disease in bone was relieved by P^{32}, but evidence in regard to specific retardation of the lesions remained questionable. The cases on which these conclusions are based are not numerous; the conclusions, however, are much the same as those quoted in a review of the literature by B. E. Hall and C. H. Watkins, of the Mayo Clinic.[2] This review mentions 273 cases of polycythæmia and also 136 patients with chronic or subacute myelogenous leuchæmia, 98 with chronic or subacute lymphatic leuchæmia and 109 with various types of acute leuchæmia. In all these cases radioactive phosphorus had been used. Hall and Watkins agree that P^{32} provides an effective means of controlling *polycythæmia vera*. The chief advantages are ease of administration, absence of

[1] *The Journal of Laboratory and Clinical Medicine*, August, 1947.
[2] *The American Journal of the Medical Sciences*, May, 1947.

radiation sickness and of symptoms of toxicity and the simplicity with which dosage can be controlled. The chief disadvantages are the cost of the material and the fact that bone marrow may be injured seriously in the case of overdosage or in the presence of unusual sensitivity of the bone morrow. In chronic leuchæmia Hall and Watkins conclude that radiophosphorus induces a remission similar to that produced by X rays, but that it has no advantages over X-ray treatment and requires a longer period to bring about a result. In acute leuchæmia, metastatic tumours, *mycosis fungoides* and xanthomatosis the isotope is found to be ineffective.

It is clear that the results obtained by the use of radioactive isotopes have been of considerable value. It is also clear that we are merely on the fringe of this kind of investigation. Doan and his co-workers expect that these isotopes will soon be much more readily available.[1] When this happens the need to temper enthusiasm with care and judgement will have to be constantly borne in mind. Gross and Leblond hold that animal experimentation must always precede clinical application, and Lawrence insists that scientific workers and clinicians using radioactive isotopes are exposed to dangers as well as patients. In the future it is devoutly to be hoped that some means will be found to give the public a balanced view of this remarkable advance in therapeutics and to prevent what are known as columnists from raising the false hopes of sufferers and their relatives.

Current Comment.

CEREBELLAR ATROPHY.

THE case of olivo-ponto-cerebellar atrophy described in this issue by C. G. Lambie, Oliver Latham and G. L. McDonald is of great interest and importance. It is an example of a group of conditions about which knowledge has been somewhat confused. Several forms stand out clearly. The first is known as Friedreich's ataxia. In this the greatest effect is on the cells of the spinal cord, but the cerebellum is involved. A case of this condition was described in this journal in February, 1917, by W. F. Litchfield, Oliver Latham and A. W. Campbell. Another type is the chronic parenchymatous cortical cerebellar atrophy. A case of this type was described in this journal on February 3, 1945, by Bruce Hall, K. B. Noad and Oliver Latham, and these authors also described a case in 1941 in *Brain*. A third variety is that exemplified by the case in the present issue—it is correctly described as olivo-ponto-cerebellar atrophy, but is also known as Marie's ataxia. This nomenclature is discussed in the present article, and cases have been reported by many writers. Another form of cerebellar atrophy, not so widely recognized, is associated with epilepsy. A case of this kind was reported in this journal on April 28, 1945, by S. J. Minogue and Oliver Latham.

The olivo-ponto-cerebellar atrophy group, though characterized by a clear-cut pathological picture, is not accompanied by any distinct clinical syndrome, and this the case reported in this issue serves to illustrate. In this instance Parkinsonian rigidity, rather than ataxia, was the outstanding clinical feature, and the observations of Wyke and McGovern on the presence of similar rigidity in lesions of the palæocerebellum in dogs may be of significance in this regard. Interest in the case report is increased by the presence of hypertension and by the onset following accident. Arteriosclerosis has often been referred to as a possible precursor of degenerative processes in cerebellar mechanisms, particularly Purkinje neurones. These vulnerable cells do not reach maturity until the second year of life and are prone to early degeneration, as are all nervous tissues which develop late. Commencing degeneration is seen normally soon after the age of forty and progresses with the years. Apparently in this case examination of the pathological material did not reveal extensive damage. What part the accident played, if any, is doubtful. The report contains no mention of the fear, delirium or rash characteristic of fat embolism, unless the nightmare and nocturnal restlessness were manifestations of cerebral irritability. Incidentally it is of interest in this regard, in view of the Parkinson's syndrome present, that the ring hæmorrhages following fat embolism were found by Grondahl to be most numerous in the basal ganglia, *cornu ammonis* and dentate nucleus. The alternative title of Marie's ataxia given to the condition described in the present case serves to draw attention to the difficulties surrounding the subject, in that Marie described an heredo-familial disease with ataxia, whereas in the present case rigidity was a prominent feature and there was no familial history of nervous disorder. At the same time, as the authors point out, sporadic cases are known to occur in any familial disease.

When attempts have been made to sort out the conditions of cerebellar atrophy emphasis has always been placed on considerations such as age at onset and heredo-familial tendencies. Many of the familial diseases of the nervous system seem to have arisen from Germany. The family dealt with by Hall, Noad and Latham in this journal came from the Leipzig region and branches of this family are known to exist in at least three Australian States. Some members of each known branch are affected by the disease.

This journal is fortunate to have had complete descriptions of four different types of cerebellar atrophy prepared for it by so discerning a pathologist as Oliver Latham.

MINERS' WELFARE IN WARTIME.

IN 1920 a semi-official Miners' Welfare Committee was constituted in Britain with the object of improving the conditions of British miners. In 1939 it became a commission which went out of office on July 12, 1946, with the passing of the *Coal Industry Nationalization Act*; a new commission was then appointed under the changed set-up. The work of the Miners' Welfare Committee and Commission was financed by the Miners' Welfare Fund, drawn largely from levies on coal output and royalties and amounting to almost twenty-five million pounds in twenty-five years. This money has been spent on pithead welfare (particularly pithead baths, canteens and cycle stores), the provision of recreation and leisure-time occupation, health schemes (with particular emphasis on rehabilitation centres), education and research.

The report of the commission's wartime work, covering the final six and a half years of its existence, has now been published. It is an interesting record of a positive approach to a task in the face of very great difficulties. In his foreword to the report, the chairman of the commission, Sir Frederick Sykes, describes the coal industry as the keystone of Britain's national prosperity and one without which its national existence would be

[1] The Acting Director-General of Health, Canberra, writes that, following the official announcement by President Truman on September 3, 1947, that the United States Atomic Energy Commission is prepared to make available radioactive isotopes to foreign countries, information has now been received regarding the arrangements for distribution. The Atomic Energy Commission has stipulated that all requests from each country must pass through one channel and that each application for any isotope must be accompanied by full particulars regarding the intended use. Details of the isotopes, which are already available, and of the arrangements which have been made for issue to Australia, can be obtained by application to the Commonwealth X-Ray and Radium Laboratory, University Grounds, Carlton, N.3, Victoria.

[1] "Miners' Welfare in War-Time", Report of the Miners' Welfare Commission for 6½ years to June 30th, 1946. Ashley Court, Ashtead, Surrey. Price: 1s. 6d.

impossible. It was especially vital during the war and had to be maintained despite all the inevitable problems. The appreciation of essentials demanded by wartime circumstances only tended to underline the fact that matters of miners' welfare were not luxuries, but indispensable to the efficient working of the industry. Some aspects of the commission's plans were, of necessity, modified, but a great deal was achieved.

An ambitious part of the programme was the building of pithead baths; this was well under way and many fine baths had been completed in 1939, but it was just not possible to carry on in the same way; current contracts were completed with many long delays and very few new contracts were placed. However, the interval allowed for useful reflection on matters of design and construction and the programme (somewhat modified) was resumed in 1945. The commission met with apathy and even opposition during the earlier years of the baths scheme, but felt that the gradually increasing demand for the baths was largely due to the good standard of the facilities provided and has refused to reduce that standard. The baths, which are used by the great majority of the miners, are a considerable advance in the field of personal hygiene. It has been the practice to include in the baths a small "first-aid" room, but its use has not been satisfactory, mainly because it is not always practicable to keep it attended. In some cases, as a practical compromise, the statutory "first-aid" room required to be provided (together with an attendant) at the colliery has been incorporated into the baths building. The Ministry of Fuel and Power is now considering the provision at collieries of facilities sufficient to deal with severe accident cases, to treat minor injuries and to afford some remedial treatment for small ills. This would require more elaborate accommodation than that at present provided and, in most cases, the attendance of a State registered nurse working under the supervision of the colliery doctor. It is intended to incorporate medical treatment centres sufficient for this scheme in all plans for future pithead baths. The commission has also been urged from various quarters to provide facilities for irradiation of the body with ultra-violet light rays ("artificial sunlight") and special "rheumatism baths". Their reluctance to spend money on irradiation facilities has been supported by a report of the Industrial Health Board of the Medical Research Council (issued in May, 1946), which was unable in extensive trials to find evidence of the alleged benefit of ultra-violet light to people in normal health. A type of aerated bath for the treatment of "rheumatic" pains has been installed in a few instances, but its therapeutic value is considered doubtful. A broader approach to the question of rheumatism has been deferred in view of a national scheme being organized by the Ministry of Health.

The provision of canteens and other arrangements for meals has apparently been a perplexing task. The miners are unpredictable in their response to any particular scheme. During the war the Ministry of Food provided extra rations for the miners, but, despite repeated requests from the Miners' Welfare Commission, would not make the rations available for consumption at home. They were provided at the pithead and the number of miners who availed themselves of the service was quite variable. The feeling of the commission is that, while light refreshment canteens should continue to be a success, the future popularity of full-meal canteens is problematical.

A good deal of energy has been devoted to improving facilities for recreation and leisure-time occupation, from both a constructive and a simple entertainment viewpoint. Wartime conditions modified plans, but the effort appears to have been worth while so far.

The amount of time and money (four and a quarter million in twenty-five years) devoted to health schemes is illuminating. In particular, the development of rehabilitation centres for miners during wartime was well in line with the extensive and progressive work in this field throughout Britain. The tremendous wartime demand for coal and the problems of manpower increased the need for efficient rehabilitation of miners; an added factor was the high accident rate in mining—six times as high as in factories. As far as possible, fractures have been treated at hospitals with specialized fracture departments, even though this might involve transfer away from the miner's home. Rehabilitation out-patient clinics have been used, when they were available and suitable, but it was found necessary to establish residential centres where rehabilitation could be handled efficiently. Suitable properties were acquired—mostly from among the "stately homes of England"—and difficulties of equipment and staff were overcome. Today the whole industry of three-quarters of a million workers is fully provided for—a remarkable and unique achievement. An honorary medical committee of eminent surgeons and physicians under the chairmanship of Sir Reginald Watson-Jones has acted in an advisory capacity. No charge is made for treatment and travelling expenses of patients are refunded. Liaison has been established with fracture treatment centres and as far as possible the same surgeon attends an injured man in hospital and at the rehabilitation centre. The treatment at the centres follows the usual lines—exercises, physiotherapy and team games with plenty of outdoor and indoor recreational activity. The average period spent at the centres in 1945 was ten and a half weeks; 33% of the men were then fit for their pre-accident work, 35% were fit for light work at the colliery temporarily, with a view to graduation to their pre-accident work, 18% were fit for light work at the colliery permanently, 5% were transferred to other industry, 1% retired permanently and 6% returned to hospital. A welfare service acts in a follow-up capacity and assists individual readjustment more particularly from the social angle. The finding of light work at collieries is not always easy, but a surprisingly small number of men have been transferred to other industry. However, the Ministry of Labour has made provision for the retraining of disabled persons unable to return to their former employment. The commission considers that an important factor in placing the disabled is the development of alternative industries in the vicinity of coal fields.

Convalescent homes have also been established, though they are not universally popular among the miners. The tendency now is to develop them along modern principles of graded recuperative treatment.

Grants have also been made to public hospitals, ambulance services and nursing services, of which use has been made, and over a million pounds have been expended for educational purposes. Of the latter amount 72% has been used wholly for mining education, 16% partly for mining and partly for non-mining scholarships, exhibitions and bursaries, and 12% for aiding non-mining education in particular circumstances.

The commission's report is well illustrated; it presents an absorbing picture of a huge task which seems to have been handled thoroughly. It is of particular interest as a part, and a most significant part, of the courageous reorganization which is changing the face of England.

A DRUG FOR INCREASING PLASMA CONCENTRATIONS OF PENICILLIN.

THE maintenance of a high plasma concentration of penicillin without the administration of excessive quantities of the drug has presented considerable difficulties. Its passage through the blood stream is very rapid. In the days when supplies of penicillin were small measures were developed for its recovery from the urine so that it might be used again. In presenting their results from the use of a new drug, "Caronamide", J. William Crosson, William P. Boger, Christopher C. Shaw and A. Kathrine Miller have briefly discussed the general problem.[1] As they point out, penicillin is rapidly absorbed from the site of its injection (in the case of the customary intramuscular injection) and rapidly excreted by the kidneys. Various measures have been suggested to increase its fleeting presence in the blood stream. An increase in the dosage and frequency of injections is an

[1] *The Journal of the American Medical Association*, August 30, 1947.

obvious means with equally obvious disadvantages in economy and the patient's comfort. Continuous intravenous infusion and intramuscular drip administration are useful, but not without technical difficulties. Some success has been achieved in slowing the rate of absorption of the drug by cooling the site of injection and by the use of a suspension of penicillin in beeswax and oil. Finally substances have been used which suppress the excretion of penicillin by the renal tubules (80% of the drug is excreted by the tubules). Iodopyrin injection ("Diodrast") and para-aminohippuric acid when administered intravenously can completely suppress the excretion of penicillin and have been employed successfully when a high plasma concentration of penicillin was essential; however, their routine use is not practicable. Benzoic acid and sodium benzoate have also been investigated in this way.

The drug now brought forward is 4'-carboxyphenylmethanesulphonanilide ("Caronamide"), "an orally effective compound of low toxicity and capable of producing a reversible inhibition of penicillin excretion by the renal tubules". Crosson and his colleagues administered "Caronamide" orally to human subjects at the same time as penicillin was given respectively orally, intramuscularly in isotonic sodium chloride solution and intramuscularly in a suspension of beeswax and oil. In each case penicillin (in appropriate form) was given for a control period both before and after its administration in conjunction with "Caronamide". The plasma concentration of penicillin was determined at suitable intervals throughout. The number of patients involved was small, but the results were too striking to be put aside lightly. Six patients were given 100,000 units of penicillin orally every four hours for six days; on the third and fourth days they were also given two grammes of "Caronamide" orally every four hours; penicillin plasma concentrations during the period of administration of the new compound were from 2·4 to 7·1 times (average 4·2) greater than those obtained when penicillin alone was administered. Eight patients were given penicillin intramuscularly and "Caronamide" orally; five who were given either 1·5 grammes of "Caronamide" every three hours or 2·0 grammes every four hours showed enhancement of penicillin plasma levels of from two to seven times those observed during control periods. Three patients given only 1·0 gramme of "Caronamide" every two hours failed to show the same degree of enhancement of penicillin plasma concentrations, but some effect of the drug was indicated, particularly towards the end of the penicillin dose response curve. Equivocal results were obtained from the study of the administration of "Caronamide" in conjunction with penicillin in beeswax and oil, but the indications are that the plasma concentration is enhanced.

This work is preliminary and requires further support. It is nevertheless striking, and the fact that the subjects acted in effect as their own controls lessens criticism related to the smallness of the series. No toxic effects attributable to "Caronamide" were noted, though there is no guarantee that these will not appear when the drug is more widely used. Crosson and his co-workers are satisfied that the effectiveness of "Caronamide" in enhancing penicillin plasma concentrations is established, and the drug is now being used in the treatment of patients at the University of Pennsylvania Hospital and at Philadelphia General Hospital. Further reports will be awaited with interest.

THE VAN DEN BERGH REACTION.

In 1916 Van den Bergh and Muller published their observations on the action of a solution of diazotized sulphanilic acid (the Ehrlich diazo reagent) on the serum of patients with various types of jaundice as well as on that of normal subjects. They showed that, when the serum of patients with obstructive jaundice was used, the red pigment azobilirubin was produced; this was termed the "direct reaction". Serum from normal subjects or from patients with hæmolytic jaundice formed azobilirubin with the diazo reagent only in the presence of alcohol or other hydroxylic substances; this was termed the "indirect reaction". Later workers subdivided the direct reaction into three forms, the immediate or prompt, the delayed, and the biphasic; the immediate form was associated with obstructive jaundice, and the delayed and biphasic forms were found to be common when the jaundice was due to liver damage. The use of this reaction became a commonly accepted aid to the clinical diagnosis of causes of jaundice. There is, however, quite a lot of confusion about the terminology and interpretation of the test, even in standard textbooks. For example, "Best and Taylor" adheres to the classification given above; the latest edition of "Osler" (1947) refers to the "direct or immediate" reaction (in obstructive jaundice), the "indirect or delayed" reaction (in hæmolytic jaundice), and the "biphasic" reaction (in toxic and infective jaundice). The latest edition of "Price" (1946) states that the test is of no value in the differentiation of different causes of jaundice. A similar conflict of opinion occurs among other standard works. However, there is a general tendency to appreciate that the diagnostic value of the test is limited.

The position of the Van den Bergh reaction has been discussed in a recent article by C. H. Gray, of King's College Hospital, London,[1] who aims at a reassessment of its clinical significance. He discusses the history of the reaction and of its modifications and seeks to discard ideas that have not been verified. He asserts that the occurrence of an immediate, delayed or biphasic direct action is related to the amount of bilirubin present and not to the type of jaundice, so that this subdivision of direct reactions is of no value whatever in the differentiation of acute hepatitis from obstructive jaundice. Furthermore, he claims that the existence of two forms of bilirubin (associated with the direct and indirect types of reaction respectively) has not been demonstrated unequivocally, and advocates that the conception should be abandoned. Instead, the relative proportions of azobilirubin formed with and without the addition of alcoholic substances (in accordance with the quantitative Van den Bergh reaction) should be determined and expressed as a direct-indirect quotient (D.I.Q.) defined as:

$$\frac{\text{final amount of azobilirubin formed in the direct reaction}}{\text{final amount of azobilirubin in the indirect reaction}} \times 100$$

For this to be of any real value it is necessary to have some constancy in the method of conducting the test. Gray discusses the available methods in detail, but concludes that the simplest and best is that of Malloy and Evelyn, in which the rate of formation of azobilirubin is followed by photo-electric means. A reading made at the end of thirty minutes (regarded as the most suitable period for routine purposes) demonstrates that the D.I.Q. values for obstructive jaundice and acute hepatitis are practically identical, and that this method (or apparently any other method) provides no means of distinguishing the two types of jaundice. In the case of hæmolytic jaundice the D.I.Q. value is generally, but not always, lower than that in obstructive or hepatogenous jaundice. A D.I.Q. value below 40 is stated to be "diagnostic of retention [that is, hæmolytic] jaundice, and a D.I.Q. above 50, although usually indicative of regurgitation [that is, obstructive or hepatogenous] jaundice, can occur in retention jaundice accompanied by liver damage. A D.I.Q. between 40 and 50 is highly suggestive of, but not absolutely diagnostic of, retention jaundice. In cases of difficulty a reticulocyte count, erythrocyte fragility estimation, search for spherocytosis, or determination of the fæcal stercobilin excretion may be essential for the clinician to establish the diagnosis".

It appears from this discussion that, despite the fact that the fallacy of older interpretations of the test has not been universally appreciated and despite the tendency in some quarters to throw the test overboard as a means of distinguishing causes of jaundice, a degree of useful information is afforded by the test, provided that the findings are viewed, as the results of almost all special investigations should be, in their right perspective in relation to all other available information.

[1] *The Quarterly Journal of Medicine*, July, 1947.

Abstracts from Medical Literature.

BACTERIOLOGY AND IMMUNOLOGY.

Coagulase in Staphylococcal Infections.

WILSON SMITH, J. H. HALE AND M. M. SMITH (*The British Journal of Experimental Pathology*, February, 1947) have studied the role of coagulase in staphylococcal infections. Most strains of staphylococci fail to coagulate guinea-pig or mouse plasma because of the absence of some activator substance in these species, but in some strains this substance is present. Coagulase activity, toxinogenicity and virulence were compared by the use of intratesticular inoculation of guinea-pigs. It was found that the strains which did coagulate guinea-pig plasma were significantly more virulent than those which failed to show this property; the presence of a coagulase effective against the host species appeared to determine a high virulence and well-developed lesion. Mice were then inoculated with staphylococci suspended in guinea-pig plasma for which they had no coagulase, and control animals were inoculated with organisms suspended in coagulable plasma; the latter showed a much higher mortality rate.

Typhoid Vaccine.

GEORGE F. LUIPPOLD, DON LONGFELLOW AND MILTON TOPOREK (*The American Journal of Hygiene*, May, 1947) have recorded the effect and effectiveness of three 0·5 millilitre doses of "T.A.B." vaccine in an effort to determine whether the present standard immunization procedure employs an optimal dosage of vaccine, and whether the occasional incapacitating clinical reaction could be avoided. Groups of medical students, who had never had enteric fever, were bled, then given three doses of 0·5 millilitre of standard "T.A.B." vaccine—the intervals between doses are not stated—and fourteen days after the last dose were bled again. The serum from these bleedings was tested for agglutinative titre and protective power in mice, and these results were compared with those from subjects given the standard course of vaccine, 0·5, 1·0 and 1·0 millilitre. Analysis of the figures showed that the modified course, while giving lower agglutinative titres, produced slightly higher protective titres, and significantly fewer and less severe clinical reactions. The authors discuss the reasons originally advanced for high agglutinative titres, and the present-day trend to use the protective antibody titre as a more reliable standard with which to work. They conclude that the modified course of vaccine is more suited to the average individual's physiological tolerance and capacity to produce immunological response.

Studies on Spreading Factors.

OSCAR HECHTER AND ELLA L. SCULLY (*The Journal of Experimental Medicine*, July, 1947) have continued their studies on spreading factors with an evaluation of the effect of serum on hyaluronidase spreading activity. Tests *in vivo* were carried out on the shaved abdominal skin of the rabbit, varying concentrations of enzyme and an indicator being injected, and the area of spread after intervals of time up to ten minutes being recorded. In some experiments, mixtures of enzyme and serum were allowed to interact in the test tube for a stated time and then injected; other mixtures were injected immediately. It was found that serum contained a substance which in five minutes could inhibit 90% of the hyaluronidase spread when the enzyme concentration did not exceed 10, or fall below 2·5 microgrammes per millilitre with constant serum concentration, provided that the interaction was allowed to take place outside the body. If the mixture was injected immediately no effect developed *in vivo*. The authors discuss the reasons for the failure of the serum factor to operate, the relation of the enzyme to the inhibitory factor, and the necessity of further work to elucidate the biological role of the factor.

Action of Succinic Acid Derivatives on Mycobacterium Tuberculosis.

P. A. MCNALLY (*The British Journal of Experimental Pathology*, June, 1947) has studied the action of monoalkyl and dialkyl succinic acids and the monoesters and monoamido derivatives of alkyl succinic acids on the growth of *Mycobacterium tuberculosis*. This work followed a suggestion that a branched chain compound from a natural source had some inhibitory action on *Mycobacterium smegmatis*. Ethyl alcoholic solutions of the anhydride of this substance, when neutralized with dilute alkali, proved to contain a mixture of isomeric monoethyl esters of monalkyl succinic acid. These compounds were synthesized by two other workers, and the present paper records results of tests for antibacterial activity against *Mycobacterium smegmatis*, *Mycobacterium tuberculosis* and *Staphylococcus aureus*. The action against the mycobacteria was greatest when the number of carbon atoms in the alkyl substituents was 13 or 15. The compounds had a considerable hæmolytic action on human red cells. The degree of bacteriostasis was diminished by the addition of serum and the medium, and while *Staphylococcus aureus* was killed in media containing these compounds, Gram-negative rods of coliform type grew normally.

The Role of Phagocytosis in Resistance.

SAMUEL SASLAW AND CHARLES A. DOAN (*The Journal of Laboratory and Clinical Medicine*, July, 1947) have studied the role of phagocytosis in resistance, as related to the age of granulocytes, following primary and reinfection studies with hæmolytic streptococci in *Macacus rhesus*. To an initial infection with this organism it had previously been noted that the response was an effective granulocytic leucocytosis; but after reinfection there was a failure to disturb the leucocyte equilibrium, although there was no change in the resistance of the animal. In this work, daily determinations of the opsonic power of the blood against the infecting organism were correlated with daily blood counts and enumeration of the lobation of the nucleus of the granulocyte as an index of its age. The changes in the blood provided the reason for the unaltered response of the animal to the infection. In the primary stage the number of leucocytes increased considerably, but the phagocytic index remained low. After secondary infection some six weeks later, although the number of circulating leucocytes did not increase, their individual power to ingest bacteria had become considerably greater. In the study of the morphology of the phagocytes in relation to their phagocytic power, it became apparent that the cell with the single-lobed nucleus consistently achieved the ingestion of the greatest number of organisms, those with a two-lobed or three-lobed nucleus came next, and the cells with a highly segmented nucleus achieved little phagocytosis. The authors suggest that a "specific humoral catalyst" is acquired during a primary infection which enables "spontaneous cellular phagocytosis" to occur, so that far fewer polymorphonuclear cells are needed to combat reinfection effectively.

Field Studies in Bacillary Dysentery.

A. H. STOCK, I. EISENSTADT, G. W. TRIPLETT, SENIOR, AND A. CATO (*The Journal of Infectious Diseases*, July-August, 1947) record the types of dysentery bacilli isolated from United States army personnel and natives in French Morocco and Italy. Some 1800 isolations from 21,000 specimens were made, and fifteen different serological types were represented. Flexner II and VI types were common, also an isolation called Lavington I; Schmitz and Sonnë types were noted; 70 cultures were not finally identified.

A. H. STOCK, W. W. TRIBBY AND A. ASHUTE (*ibidem*) describe studies on the pathogenicity of type Lavington dysentery bacillus recorded in the previous paper. The clinical disease was severe and sudden in onset, the stool was typical, and cultures of non-lactose-fermenting organisms were rich; the strain fermented mannite, produced indole, and did not agglutinate with available types of antiserum, but did so with homologous antiserum produced by injecting rabbits with the strain. The epidemic due to this strain appeared in a replacement depot, and a mess sergeant, found to be a carrier, admitted to an attack of diarrhœa for which he had not sought treatment. It was recorded that, in spite of sulphaguanidine treatment, many patients with this strain carried it for as long as five weeks.

A. H. STOCK, A. G. KARLSON, W. W. TRIBBY AND J. H. HILL (*ibidem*) describe the epidemic of bacillary dysentery in the Atlantic Base Section in French Morocco in 1943. This was the one due to type Lavington dysentery bacillus, whose pathogenicity was studied in the previous paper. The hygienic measures instituted and the laboratory tests undertaken supplied strong evidence that a person to person contact was responsible for spread, and that food handlers were particularly important. Flies trapped in latrines failed to produce cultures of the infecting organism.

A. H. STOCK, F. B. WARNER AND H. S. LEVINSON (*ibidem*) studied the distribution of types of dysentery bacilli in United States troops before, during and after the assault on the Gothic line. A survey of carriers, carried out on sample personnel groups in five divisions, yielded positive results in 0%,

2·0%, 3·8%, 3·5% and 6·4% of the group members, all the carriers being widely distributed; the division which had no carriers had not been in active combat. A small survey amongst the civilians in the area showed a carrier rate of 6%. Irregular outbreaks of diarrhœa amongst combat troops occurred during the assault on Bologna, and once again the authors concluded that the infected food handler played a major part in the spread of dysentery.

Amino Acid Content of Viral Particles.

C. A. KNIGHT (*The Journal of Experimental Medicine*, August, 1947) has studied the amino acid content of highly purified viral particles of influenza A and B, in an attempt to discover a basis for the similarities and differences between strains which are identical in their infective manifestations and gross chemical characters. Assays for 17 amino acids were carried out, and approximately the same amounts of alanine, aspartic acid, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine and valine were found. Significant differences were recorded, however, in the amounts of arginine, glutanic acid, lysine, tryptophane and tyrosine present in each of the strains. The authors believe that these differences may in part explain the differing immunological behaviour of the two strains of influenza virus.

HYGIENE.

The Control of Roaches and Bedbugs with DDT.

ROBERT L. STENBURG (*Public Health Reports*, May 9, 1947) states that experiments were carried out on the effectiveness of DDT against the German roach *Blattella germanica* and the American roach *Periplaneta americana*. It is probable that diseases may be mechanically transmitted by these insects. Four standards of infestation were used. These were as follows: (i) A: no roaches evident; (ii) B: one to six roaches per room evident; (iii) C: six to sixty roaches per room evident; (iv) D: too numerous to count. The following methods were used: (i) overall spraying with 2·5% DDT xylene-Triton X-100 emulsion to give a deposit of 100 milligrammes of DDT per square foot; (ii) spraying with 5% and 10% solutions of the above to give 200 to 400 milligramme deposits of DDT per square foot respectively; (iii) application of a 10% DDT dusting powder to obvious roach resting places; (iv) combined spraying with 5% solution and dusting with 10% powder. A four-gallon knapsack sprayer with an atomizing nozzle, producing a flat-fan spray pattern of approximately 50° with a discharge rate of one-tenth of a gallon at 40 pounds' pressure, was the most suitable. In the fourth method all surfaces exhibiting cracks were sprayed with 5% DDT spray, and as the roaches emerged, their resting places were located and dusted with 10% DDT dusting powder. An application of the same DDT dusting powder was made under all furniture and in places where the floor was not regularly swept. This was the most effective method and the standard of infestation with American roaches was reduced from D to A or B within one week after treatment. That with German roaches was reduced from D to B within one week and to A after four weeks' interval in two-thirds of the places treated. Special care was taken to protect all food and dishes before spraying. DDT is the most effective insecticide yet used against bedbugs. In these experiments 2·5%, 5% and 10% solutions of DDT were used as follows. (i) Mattresses were sprayed on both sides and around the edges. (ii) Mattresses and bed-springs were sprayed. (iii) Mattresses, bedsteads and bed-springs were sprayed. (iv) Entire beds and walls were sprayed. (v) Walls, ceilings, chairs, divans and beds were sprayed. All methods were found to give complete control of bedbugs for the duration of the investigation—a period of sixteen weeks. Surfaces were given an even application, just to wet the surface without the solution's running off.

Cheese and its Relation to Disease.

F. W. FABIAN (*American Journal of Public Health and The Nation's Health*, August, 1947) considers that cheese does not receive the attention from public health officials that it deserves. It is a highly nutritive food and should be free of disease germs. There have been reported in the United States and Canada since 1883, 59 epidemics with 2904 cases of disease and 117 deaths. There is every reason to believe that this represents only a part of the disease caused by cheese. The organisms most commonly associated with cheese-borne infections are members of the salmonella group such as *Salmonella aertrycke, schottmülleri, typhosus, suipestifer, typhimurium* and *choleræ suis*; staphylococci such as *Staphylococcus albus* and *aureus*; members of the brucella group: *Brucella melitensis* but not *abortus*; and *Clostridium botulinum*. There are no reports in the literature of undulant fever due to *Brucella abortus*, although cheese doubtless is made from milk containing an abundance of these bacteria. Likewise, there are no reports in the literature of septic sore throat or scarlet fever due to streptococci despite the fact that these organisms must be present at times in raw milk made into cheese. *Escherichia coli* is not considered as a cause of cheese poisoning. In Europe several investigators have considered it responsible for the toxic symptoms of illness due to cheese. Contrary to the opinion of many cheese makers, pasteurized milk makes a consistently higher scoring and better flavoured Cheddar cheese than cheese made from raw milk. Cheese made from pasteurized milk can be ripened in about half the time required to ripen cheese made from raw milk, since it can be held at a higher temperature. Experiments made by seeding pathogens into milk and making the milk into cheese show that the pathogens die out more rapidly at the higher temperatures. Seven American States and Canada now require cheese to be made from pasteurized milk or cream or to be held in storage for periods ranging from sixty to one hundred and twenty days in lieu of pasteurization. The sixty-day holding period is considered too short a time, since pathogens may survive this storage period, especially if the cheese is held at low temperatures, 40° to 50° F. A ninety-day holding period is considered preferable and one hundred and twenty days still better. All milk used in making soft cheeses should be required to be pasteurized, since many soft cheeses cannot be held for sixty days without being spoilt or deteriorating in quality.

Microbiology of Spray-Dried Whole Egg.

MATHILDE SOLOWEY AND VERNON H. MCFARLANE (*American Journal of Public Health and The Nation's Health*, August, 1947) state that, following reports of the British Food Mission which drew attention to the fact that organisms of the salmonella group were being isolated from dried egg powder received in the British Isles for food purposes, an investigation was carried out concerning the incidence and types of salmonella organisms in spray-dried whole egg powder manufactured in the United States of America between September, 1943, and January, 1945. Organisms of the salmonella group were isolated from 35% of 5198 samples of spray-dried whole egg powder obtained from 100 dehydration plants between September, 1943, and January, 1945. The incidence of salmonella organisms in samples examined from individual plants ranged from 0% to 71%. Fifty-two salmonella types were identified, five of which, *Salmonella pullorum, Salmonella oranienburg, Salmonella montevideo, Salmonella tennessee* and *Salmonella anatum*, made up 73% of those isolated. Culturally, morphologically, biochemically and serologically the 52 types are in every way similar to those isolated from human beings and animals. The types that occur with greater frequency in dried eggs are among those that commonly occur in human and animal infections. The frequency distribution of the salmonella types isolated from dried eggs is not the same as that of the types isolated from human beings.

Selenium Fume Exposure.

MARSHALL CLINTON, JUNIOR (*The Journal of Industrial Hygiene and Toxicology*, July, 1947), reports that a group of workers in a plant engaged in smelting scrap metal were suddenly and unexpectedly exposed to intensely irritating, unpleasant reddish fumes, which smelled like sour garlic, when an aluminium furnace was charged with aluminium rectifier plates coated with metallic selenium. The unpleasant irritating effects of these fumes limited exposure to the brief period necessary to get out of the contaminated atmosphere, so that no significant absorption of selenium took place. Exposed workers noticed that the fumes produced an immediate intense irritation of the eyes, nose and throat, followed by a severe burning sensation in the nostrils, dryness of the throat and a severe frontal headache. Two severely affected workers were put into hospital, treated conservatively, and discharged two days later with no signs or symptoms. The absence of selenium in the urine and the absence of the characteristic odour of methyl selenide in the breath suggested that no selenium absorption had taken place. The author recommends that old rectifier plates be discarded, as selenium not only creates a moderate fume hazard, but also contaminates the aluminium.

Bibliography of Scientific and Industrial Reports.[1]

THE RESULTS OF WAR-TIME RESEARCH.

During the war a great deal of research was carried out under the auspices of the Allied Governments. It has been decided to release for general use a large proportion of the results of this research, together with information taken from former enemy countries as a form of reparations. With this end in view, the United States Department of Commerce, through its Publication Board, is making a weekly issue of abstracts of reports in the form of a "Bibliography of Scientific and Industrial Reports". This bibliography is now being received in Australia, and relevant extracts are reproduced hereunder.

Copies of the original reports may be obtained in two ways: (a) Microfilm or photostat copies may be purchased from the United States through the Council for Scientific and Industrial Research Information Service. Those desiring to avail themselves of this service should send the Australian equivalent of the net quoted United States price to the Council for Scientific and Industrial Research Information Service, 425, St. Kilda Road, Melbourne, S.C.2, and quote the PB number, author's name, and the subject of the abstract. All other charges will be borne by the Council for Scientific and Industrial Research. (b) The reports referenced with an E number may be obtained in approved cases without cost on application to the Secondary Industries Division of the Ministry of Post-War Reconstruction, Wentworth House, 203, Collins Street, Melbourne, C.1. Copies of these are available for reference in public libraries.

Further information on subjects covered in the reports and kindred subjects may be obtained by approaching the Council for Scientific and Industrial Research Information Service, the Secondary Industries Division of the Ministry of Post-War Reconstruction, or the Munitions Supply Laboratories (Technical Information Section), Maribyrnong, Victoria.

PB 40978. SHIH, LU CHANG. Destruction of cysts of *Entamœba histolytica* in drinking water. Monthly Progress Report, Nos. 1-6. March-August, 1942. 6 pp. Price: Microfilm, $1.00; Photostat, $1.00.

These progress reports summarize the results of tests in which several different compounds were used to kill *Entamœba histolytica* cysts which were suspended in drinking water and sewage and other contaminated waters. The tests were conducted at various temperature levels. When gaseous chlorine was used, it was found that a higher concentration of organic matter in the water required more chlorine. Copper sulphate in concentrations of 5 to 20 p.p.m. had practically no effect on the cysts. Several experiments showed the effectiveness of chloramines prepared from gaseous chlorine and ammonium hydroxide and from gaseous chlorine and ammonium chloride. The effects of pH, oxidation potentials and contact time were noted. Several tables are included. These progress reports cover work performed under the auspices of the Committee on Medical Research of the Office of Scientific Research and Development (OEMcmr-33).

PB 47069. WALKER, JAMES, JUNIOR. The pathological physiology of the extensive superficial burn. No date. 18 pp. Price: Microfilm, $1.00; Photostat, $2.00.

This report summarizes the physiology of the severe burn in the light of recent research. Topics considered in the report are local effects; local therapy; systemic effects, including shock, delayed visceral damage or "toxæmia", and period of repair; systemic therapy including maintenance of the nitrogen balance and protection against infection. Bibliography. This report is a contribution from the Medical Division, Edgewood Arsenal, Maryland.

PB 25358. MACY, R. Fundamental study of toxicity. Partition coefficients between various oils and various aqueous phases at 20° C. (Edgewood Arsenal Chemical Division Report 444, Supplement 1.) March, 1932. 16 pp. Price: Microfilm, $1.00; Photostat, $2.00.

This supplement to the Chemical Division Report 444 (PB 25575) describes work done after the completion of that report. The purpose of that report was to collect data with which to test the Overton-Meyer theory of narcosis. Since many substances were found for which there is no apparent relation between the partition coefficient and the Overton-Mayer constant, further information was sought in regard to other factors which influence distribution between oil and water. This supplement consists of experiments for the following: difference in partition coefficient between olive oil and water, and that between olive oil and physiological salt solution; partition coefficients between lard oil and water, menhaden oil and water, olive oil and water, olive oil and blood serum; and the coefficients of some nitrochlorobenzenes between olive oil and water. Tables are included. See also Supplement No. II (PB 25359).

PB 48091. VOGE, A. LAW, comp. Biological applications of supersonics (ultrasonics). (NAVSHIPS Tech. Lit. Res. Series 1.) October, 1941. 6 pp. Price: Microfilm, $1.00; Photostat, $1.00.

This bibliography lists seven treatises, thirty-six periodical articles published in 1928-1938 cited by Bergmann and two periodical articles located by the author and published in 1938 and 1940 respectively. Many of the references are foreign.

PB 25575. MACY, R., AND EHRENFELD, D. Fundamental study of toxicity. Partition coefficients between olive oil and water at 20° C., with addendum. (Edgewood Arsenal Chemical Division Report 444.) February, 1928. 76 pp. Price: Microfilm, $2.00; Photostat, $6.00.

This report covers the investigation of the partition coefficients (at 20° C.) of sixty-six chemical compounds between olive oil and water, and of one compound between air and water. The compounds studied are of widely varied chemical and physical properties. Thirty-three of the compounds have been classified as narcotics, twelve have been classified as lachrymators; the other twenty-one include toxics, analgesics, and relatively inactive compounds having a chemical structure similar to some of the others which have marked physiological properties. It was concluded that there was no apparent direct relationship between partition coefficients and lachrymatory concentrations. Testing equipment is described and tables and bibliography are included. The addendum states that the partition coefficient of methyl alcohol between olive oil and water averages 0·014. See also Supplements I and II to this report (PB 25358 and PB 25359).

PB 25359. MACY, R. Fundamental study of toxicity. Migration of toxics through an oil-water interface at 20° C. (Edgewood Arsenal Chemical Division Report 444, Supplement 2.) May, 1932. 27 pp. Price: Microfilm, $1.00; Photostat, $2.00.

This report supplements Chemical Division Report 444 and Supplement I (PB 25575 and PB 25358). The supplementary work described in this report can be divided under the following headings: rate of hydrolysis of compounds migrating from olive oil to water; rate of migration of compounds from water to olive oil; additional data on the rate of migration of chloro-acetophenone and mustard gas from olive oil to water; rate of penetration of HCN gas through a thin layer of paraffin oil on water. The method of testing and tables of test results are included (HCN equals hydrocyanic acid.)

PB 26960. MACY, R. Fundamental study of toxicity. The surface tension at an olive oil-water interface. (Edgewood Arsenal Chemical Division Report 451.) May, 1932. 50 pp. Price: Microfilm, $1.00; Photostat, $4.00.

The effect of dissolved narcotics on the surface tension of olive oil and of water was investigated in order to find whether there is a relation between surface tension and narcosis. It was also intended to determine whether narcotics as a class are similar to calcium salts in their effect on olive oil and water emulsions. Surface tension and interfacial tension measurements were made on olive oil and water solutions of a selected group of narcotics. The measurements were made by microscopic observations, substitution of narcotics for calcium chloride in olive oil-water emulsions, Du Noüy tensiometer, drop number, and effect on the inversion point of olive oil-water emulsions. It was found that narcotics as a class have only a negligible effect on the surface tension at the interface between olive oil and water and that narcotics do not behave like calcium salts in stabilizing a water-in-oil emulsion. Graphs and a bibliography accompany the report.

PB 4037. PHILIPS, FREDERICK S., GILMAN, ALFRED Z., AND CRESCITELLI, FREDERICK N. Studies on the pharmacology of DDT (2,2 bis-parachlorophenyl-1,1,1 trichloroethane). II. The sensitization of the myocardium to sympathetic stimulation during acute DDT intoxication. (Chemical Warfare Service. Medical Division Report 51.) 1945. 15 pp. Price: Microfilm, 50c.; Photostat, $1.00.

The experiments described in this report were undertaken to explain the occurrence of ventricular fibrillation in laboratory animals following acute intoxication with DDT. It is concluded that DDT both sensitizes the myocardium and causes sympathetic discharge. The latter may be reflex, but more probably is the result of direct hypothalamic stimulation. It is this dual action which is responsible for the onset of ventricular fibrillation.

[1] Supplied by the Information Service of the Council for Scientific and Industrial Research.

PHILIPS, FREDERICK S. A review of the biological properties and insecticidal applications of DDT. (Chemical Warfare Service. Medical Division Report 13.) Off. Pub. Bd., Report, PB 4045. 1944. 31 pp. Price: Microfilm, 50c.; Photostat, $3.00.

A survey of investigations pertaining to the military uses of the insecticide DDT and of studies to determine: (i) the toxicology of DDT in species affecting military operations; (ii) the mechanism of action of DDT; (iii) the results of pharmacological investigations in man and other mammals; and (iv) the methods in use for dispersal of the agent in practical insect control. Bibliography contains 59 entries.

PHILIPS, FREDERICK S., AND GILMAN, ALFRED Z. Studies on the pharmacology of DDT (2,2 bis-parachlorophenyl-1,1,1 trichloroethane). I. The acute toxicity of DDT following intravenous injection in mammals. (Chemical Warfare Service. Medical Division Report 50.) Off. Pub. Bd., Report, PB 4038. 1945. 14 pp. Price: Microfilm, 50c.; Photostat, $1.00.

Purpose of the experiments reported here was to develop a technique for the intravenous administration of DDT and thereby (i) to determine the absolute toxicity of DDT for various mammals, and (ii) to study the time of onset of action of DDT and the possible role of intermediaries of the metabolism of DDT in the manifestation of toxic action and duration of action by DDT. The symptoms of acute DDT intoxication in mammals consist predominantly of muscle tremors and tonic and clonic convulsions. These symptoms are probably caused by DDT itself rather than a metabolic transformation product.

PB 4036. PHILIPS, FREDERICK S., GILMAN, ALFRED Z., AND ST. JOHN, ELLEN. Studies on the pharmacology of DDT (2,2 bis-parachlorophenyl-1,1,1 trichloroethane). III. The treatment of acute DDT intoxication in experimental animals. (Chemical Warfare Service. Medical Division Report 52.) 1945. 15 pp. Price: Microfilm, 50c.; Photostat, $1.00.

While the toxicity of DDT is so low that poisoning is not anticipated provided reasonable precautions are observed, it is essential that therapeutic measures for treatment of incidental poisoning be available. The effectiveness of a series of central nervous system depressants in the control of acute DDT intoxication in rats, cats, dogs and monkeys has been studied. Of the various agents evaluated, phenobarbital proved the most effective antagonist of the toxic effects of DDT.

PB 37214. LOECKLE, W. E. *Über die Wirkung von Schwingungen auf das vegetative Nervensystem und die Sehnenreflexe* (The effect of vibrations in regard to the autonomic nervous system and the patellar reflexes). (*Deutsche Luftfahrtforschung* FB 1283.) September, 1940. 34 pp. Price: Microfilm, $1.00; Photostat, $2.00.

This study deals with the effect of mechanical vibrations in regard to patellar Achilles and biceps reflexes as a function of the central nervous system. Degree and speed of the reflex decrease depends upon frequency, amplitude, endurance of vibration and tested person. The report expresses new viewpoints on the physiological effect of mechanical vibrations, observations on illness causing vibrations and technically deciding factors.

PB 48306. EBERSPACHER (J.), ESSLINGEN-NECKAR, GERMANY. Report on artificial limb. (In English and German.) No date. 8 pp. Price: Microfilm, $1.00; Photostat, $1.00.

This is a one-page report in German with English translation on the aluminium artificial leg developed by the Institut für Medizintechnik (Prof. Dr. techn. H. Wögerbauer), Munich, under the initiative of the Bavarian Red Cross and manufactured by the firm of J. Eberspächer, Esslingen-Neckar. A drawing shows the fundamental construction of the artificial leg OPR 13 II which has been replaced by a new type OPR 14. It was developed for mass production, beginning with 2000 legs monthly at the end of 1946 or beginning of 1947. Beginning in June, the firm was to produce a preliminary serial with provisional tools. Enclosures (in German) give lists of material needed for 100 legs OPR 14 and sources of supply. Three photographs show finished artificial legs.

PB 42740. UNGLEY, C. C. Research and development of life-saving equipment. Medical aspects of shipwreck. Report on visit to occupied Europe, July, 1945. (With Addendum, March, 1946.) (BIOS Final Report 494, Item 24.) September, 1945. 59 pp. Price: Microfilm, $2.00; Photostat, $4.00.

The report describes visits to individual targets in Germany in order to obtain information regarding the effects of cold and immersion, starvation, dehydration and drugs on internees of the concentration camps. The following is a list of the institutions visited, giving their location and the subject of visit: Eckernforde, German life-saving equipment (no report given); Hassee Naval Hospital, Kiel, cold injury; Malente marine lazarett, Malente near Plön, cold injury; Belsen concentration camp, Belsen, starvation and dehydration; 21 Army Group (Medical), Herford, cold injury; Hirnforschungs Institut and Farm Weisbacharhof, Neustadt in Schwarzwald, CO_2 poisoning; University of Innsbruck, Innsbruck, cold injury, drugs; Physiological Laboratory of the Gebirgssanitätsschule, St. Johann in Tirol, cold injury; the Institut für Luftfahrtmedecin, Freising, north of Munich, general effects of cold and immersion; Helmholz Institute, Brannenburg, south of Munich, general effects of cold; Pathological Institute, Münster, cold injury; Physiologische Institut of Göttingen University, Göttingen, general and local effects of cold. The findings of Dr. Jurgen Aschoff in this field are also described. The appendix includes a list of documents and pamphlets which were obtained, reports of Allied conferences, a list of miscellaneous typewritten manuscripts and a list of journals, all pertaining to the subject under investigation. Some graphs and diagrams illustrate the reports.

PB 37536. STRUGHOLD, H. *Höhenwirkung nach Unterbrechung der Sauerstoffatmung in grossen Höhen, Analyse und praktische Folgerungen* (Altitude effect after interruption of oxygen respiration in high altitudes, analysis and practical consequences). (*Deutsche Luftfahrtforschung* FB 1208.) April, 1940. 14 pp. Price: Microfilm, $1.00; Photostat, $1.00.

The *"Luftfahrtmedizinisches Forschungsinstitut* of the *Reichsluftfahrtministeriums,* Berlin", tested in a 7000 m. altitude and above the interruptive reaction of interrupted oxygen respiration. The aeroembolism increases with higher altitudes and leads finally to sudden death. The time of undisturbed performance after interrupted oxygen respiration and its significance is described. Bibliography and explanatory drawings are enclosed.

PB 42296. REIHER, H., AND MEISTER, F. J. The sensitiveness of the human body to vibrations (*Empfindlichkeit des Menschen gegen Erschütterung*). (AAF T-2 Translation 616.) August, 1946. 15 pp. Price: Microfilm, $1.00; Photostat, $1.00. (Limited supply Mimeograph, 50c.)

This report describes experiments to determine the effect of vertical and horizontal vibrations upon the human body. A platform was set into sinusoidal vertical and horizontal vibration of various amplitudes. The persons to be observed lay or stood on this platform so that the vibration was either along or across their body axis. The findings are expressed in diagrammatic form and show that no single quantity characterizing the vibration (amplitude, frequency, velocity or acceleration) expresses basically the strength of sensation. The threshold of vibratory perception depends on a constant value of the product of the frequency and amplitude, and thus on a constant vibratory velocity; while the characteristic of the boundary of danger varies with the case under consideration. A table, graphs, diagrams of the testing apparatus and a bibliography are included. This is a translation of a German article which appeared in *Forschung* (VDI, Berlin), Volume II, Number 11, in November, 1931.

PB 38268. RUFF, S. *Untersuchungen an Flugzeugen verschiedener Muster zur Festellung der Belästigung der Besatzungen durch Auspuffgase* (Investigation of various aircraft models to determine the annoyance caused by exhaust gases upon crew members). (ZWB *Forschungsbericht* 142.) October, 1934. 15 pp. Price: Microfilm, $1.00; Photostat, $1.00.

The "DVL E.V. Berlin-Adlershof" investigated various aircraft models in regard to severe annoying exhaust gases. After long flights, crew members complained of nausea, vomiting, headaches and pressure in the epigastrium. Several aircraft were flown and the pilot and observation compartment were examined in relation to the carbon dioxide content of the harassing exhaust gases. Air specimens at various flying positions were quantitatively tested with special reference to carbon dioxide. Photographs and tables of data are included. In German.

E. 333. DUTCHER, R. ADAMS.[1] Research activities of the Kaiser Wilhelm Medical Research Institute at Heidelberg. Off. Pub. Bd., Report, PB 1248. 1945. 7 pp. Price: Photostat, $1.00; Microfilm, 50c.

This report contains information on the following research projects undertaken at this institute: vitamin *E*, fortification of oleomargarine, cheese quality, antiseptic compounds, beverage from mountain ash berries, method for preparing riboflavin from milk whey. It was found that rats receiving a diet containing protein of poor biological value showed evidence of liver injury. Kuhn reported that vitamin *E* therapy had been successful in a number of cases. Experiments on cheese quality suggest future studies on other vitamins. An outgrowth of work on anti-biologic substances was the discovery of the bactericidal properties possessed by bromo-hydroxybenzyl derivatives. A new beverage not unlike lemon juice was made from mountain ash berries. Method of preparing riboflavin from whey is less expensive and eliminates use of obnoxious pyridine.

[1] This report (referenced with an "E" number) may be obtained by approved applicants without cost from the Secondary Industries Division of the Ministry of Post-War Reconstruction, 203, Collins Street, Melbourne, C.1. Copies are also available for reference in public libraries.

Medical Societies.

MELBOURNE PÆDIATRIC SOCIETY.

A MEETING of the Melbourne Pædiatric Society was held on May 14, 1947, at the Children's Hospital, Melbourne, DR. A. P. DERHAM, the President, in the chair.

Osteogenesis Imperfecta.

DR. A. MURRAY CLARKE showed a female child, aged three years, suffering from *osteogenesis imperfecta*. This case will be reported in full in a future issue of the journal.

Dermato-Myositis.

DR. ROBERT SOUTHBY showed a male child, aged ten years, with dermato-myositis. He said that the history dated back to January, 1947, when the child had had three attacks of pain in the shoulders, shifting from one to the other. In early February, 1947, he had had a febrile illness, diagnosed as acute tonsillitis. About that time he had complained of soreness and stiffness in the hands, pains in the feet, and stiffness of the feet and calves. The impression was then gained that he was suffering from rheumatic fever. About the middle of February it had been noticed that he had weakness of the extensors of both his wrists and ankles. In late February tonsillectomy was performed. Dame Jean Macnamara had found, in addition to weakness of the extensors, a general slowness in all muscular responses; she also elicited a history of contagious abortion in the child's father's milk herd, as well as contact with lead paints.

The patient had been admitted to hospital on March 22, 1947, and the above findings were substantiated. It was also noted, as Dr. Macnamara had pointed out, that the skin seemed to be adherent to the underlying muscles in the forearms and legs. At the time of admission he had improved to some extent. His gait had become normal, and only a slight weakness of his ankle extensors was noted. X-ray examination of the chest showed enlargement of the hilar glands, and accentuation of the lung markings. The result of an agglutination test for *Brucella abortus* was negative. Microscopic examination of the urine revealed occasional leucocytes only. The hæmoglobin value was 92%. The white cells numbered 15,650 per cubic millimetre, of which 38% were polymorphonuclear leucocytes, 24% lymphocytes, 3% macrocytes, and 35% eosinophile cells. The film showed no evidence of basophilic stippling, and the number of reticulocytes was within normal limits.

Dr. Southby went on to say that Dr. Graeme Robertson had seen the patient in consultation on April 1, 1947. He considered that the child had some form of myositis, and probably could be classed in the dermato-myositis group, although the dermatitis element was lacking in the history. His observation was based on the fact that all muscles of the arms felt unduly firm, and marked tenseness and weakness of the wrist flexors were present. As the child was improving and in good general health, he had been sent home on April 4, 1947, with instructions to wear plaster boots, and splints for his arms at night. He was readmitted on May 13, 1947. In the interval he had been very well; he had been sleeping well, and his appetite had been excellent. The night boots had been comfortable, but the night hand splints quite often caused him discomfort and had to be adjusted. Both forearms, and to a lesser extent, the legs, appeared to be abnormally sensitive to painful stimuli. His wrists and fingers were very stiff in the mornings, so far as flexion was concerned; but this wore off as the day advanced. He experienced some difficulty in walking up and down stairs; otherwise he was a normal, healthy boy. He had been seen by Dr. Robertson again on the morning of the meeting. He considered that the child had improved since his last examination. Flexion of the wrist and fingers was still limited by the tenseness of the flexor muscles, power within the permissible range being good. Extension of the wrists was freer than before, the flexors being longer than previously. The muscles still felt hard and tense, although that was less than before. In the latest differential white cell count 32% had been found to be polymorphonuclear leucocytes, 30% lymphocytes, 4% macrocytes, and 34% eosinophile cells.

In presenting the boy suffering from dermato-myositis, Dr. Southby explained that, although the condition had rarely been shown at meetings of the society, there was a rather voluminous literature relating to the subject, and the condition was apparently more often seen than was generally thought. The main reason for bringing the boy before the members of the Pædiatric Society was to indicate the insidious manner in which the disease could first manifest itself. For example, should the dermatitis element predominate, the skin lesions might simulate such entities as *erythema multiforme*, *erythema nodosum*, various toxic erythemata, urticarial and eczematous conditions, and in more severe cases, hæmorrhagic areas closely akin to some of the purpuras. If, on the other hand, the myositis was the more prominent feature, it might closely resemble acute rheumatism, on account of the pain and fever and disability, but was distinguished by the absence of actual joint involvement and the presence of swelling and tenderness in the muscles. Poliomyelitis might be confused with the soreness and weakness, but with the condition under discussion there was generally rapid progress to paralysis, and there would be other signs of nervous system involvement. The myopathies and muscular dystrophies might also be confused in the early stages, but the "doughy" œdema of the muscles and the feeling that one might be handling a piece of bacon soon revealed the true nature of the trouble. Should the œdema be outstanding at the onset, the patient might appear to be suffering from nephritis (especially if albuminuria was present, which was not infrequently the case), myxœdema, or even the œdema accompanying some of the vitamin deficiencies.

Dr. Southby said that in the boy under consideration the condition had commenced, as would be noticed from his clinical history, with a "rheumatic-like" onset with the aching pains in the shoulders and upper part of the arms and disinclination to move the limbs on account of the pain, although there was no true arthritis present. He had later manifested some degree of what appeared to be double wrist drop and double foot drop, and, as there was a history of contact with lead paint, peripheral neuritis had to be excluded; on close inspection it was evident that the inability to dorsiflex the hands and the feet was due to the tense œdema and the discomfort and that there was no true nerve involvement. His blood picture showed eosinophilia of 35%, but there was no stippling of the red cells. As trichinosis was unknown in Australia, the condition hardly merited consideration, and, further, patients suffering from that disease usually manifested some signs of diaphragmatic or ocular paresis. A further point of interest in the particular patient under discussion was that he lived on a dairy farm, and recently there had been cases of contagious abortion amongst the dairy herd. Laboratory tests, however, showed no evidence of brucella infection.

Dr. Southby went on to say that dermato-myositis might run an acute, subacute, or chronic course of weeks, months or years respectively. The mortality rate was often as high as 50%. Some patients ultimately recovered completely, some were left with varying degrees of disability depending upon the amount of actual muscle damage, whereas others might survive, but remain permanently crippled. In some cases the condition appeared to drift gradually into a true scleroderma, and in others it slowly progressed to a final clinical picture of *calcinosis universalis*. By a strange coincidence, during the week before the meeting, there had appeared accounts of dermato-myositis in three different journals which came to hand through the mail.

With regard to treatment, Dr. Southby remarked that there was little to be done apart from rest in bed, good nourishment, efficient nursing, and orthopædic treatment to help the weakened muscles, and the prevent deformities occurring during the period of inactivity. A further prophylactic measure, directed towards the possible sequel of *calcinosis universalis*, was the administration of acid sodium phosphate in doses of sixty grains three times daily over a fairly long period, and this was well tolerated by most children. In the event of an acute exacerbation with fever, both sulphonamides and penicillin should be used in maximum dosage.

DR. VERNON COLLINS said that he could recall an adult patient afflicted with the disorder whose temperature had been elevated for six months, and in whom there had been no response to penicillin whatever. The presenting symptom was weakness, and the case had proved very baffling in the early stages, especially when vague aches and pains appeared. It was not surprising that subjects of the disorder were often labelled as suffering from neurosis.

DR. LES WAIT said that he had shown a patient with scleroderma two years previously. The child had come from Fairfield, and the skin had become very thick and hard. On the same evening, Dr. Arthur Day had shown two children with morphœa. Dr. Wait said that his patient had had a mask-like face, as well as thickened skin, but no muscle changes were demonstrable. The child had been in Fairfield Hospital with scarlet fever and infected tonsils, and improvement set in after tonsillectomy. Dr. Wait asked Dr. Southby if the two conditions were the same.

DR. JOHN COLEBATCH asked if there was any allergy in the family in view of the eosinophilia. He asked whether *periarteritis nodosa* fitted the picture at any stage. He also asked whether there was any relationship to sclerema, and whether there had been any suggestion in the literature that cold played any part in the ætiology.

Dr. Southby, in reply, said that penicillin therapy had been tried because the patient was febrile, and a recent article had appeared in the literature on the subject. In the acute stages some response might be expected. In answer to Dr. Wait, he said that most authorities appeared to line up morphœa and scleroderma in one group. The clinical manifestation depended on which part bore the brunt of the infection, if it could be called an infection. In answer to Dr. Colebatch, he said that there was no definite family history of allergy. Dr. Southby said that he could recall seeing several children with high eosinophilia. One had eosinophilia of 60%; he was from the country, and the results of all investigations proved negative. At a later date the child had suddenly had an attack of distressed breathing, followed by a giant urticarial rash. It was thought that probably a hydatid cyst had ruptured, but radiological examinations had provided no evidence of that condition, and subsequently the child had run the course of a severe asthma with allergic skin manifestations. In the patient presented there had been no history of helminthic infection. Dr. Southby said that he still felt inclined to regard the child as a "starter" for an allergic state. In answer to Dr. Colebatch's second question, Dr. Southby said that if *periarteritis nodosa* had come into the picture, he would have expected more pain from time to time. Pain was present at one stage only, when the condition simulated a rheumatic infection. In answer to Dr. Colebatch's third question, Dr. Southby said that he did not think that there was any relationship to cold. Scleroderma and sclerema were distinct entities. Sclerema occurred in weakly newborn babies, often premature, or the offspring of a mother in a toxic state. These conditions were more often met with during a sudden spell of cold weather, and in hospitals with a limited staff and facilities for keeping babies warm. The patients were difficult feeders, and were often placed in a pantry under the stairs and maybe left to fend for themselves with a bottle perched on a pillow. It became more and more difficult to get such infants to feed, and they became suddenly ill and rigid like marble, and eventually died from bronchopneumonia. They passed through the stage of œdema of inanition to scleroderma, and later the condition turned to sclerema with solidification of the subcutaneous fat. The condition was quite distinct from scleroderma.

Osteogenic Sarcoma.

DR. RUSSELL HOWARD showed a male child, aged twelve years, with a history of an intermittent swelling at the lower end of the left femur, of six months' duration. X-ray examination revealed the typical appearances of bone sarcoma. X-ray therapy had been instituted at the Royal Melbourne Hospital by Dr. Kaye Scott, and had then been concluded. Radiographic examination showed the absence of any sign of activity of the bony lesion, and considerable bone regeneration in it. The lungs showed no evidence of metastases. The child was well and was walking on the affected limb. The patient was being shown to stimulate discussion concerning further treatment. The particular points at issue were whether and at what level amputation should be performed. It was generally agreed that the risk of recurrence in those cases was sufficiently great to make amputation essential. Dr. Howard said that he proposed to perform disarticulation at the hip joint, as he felt that, once amputation was agreed upon as necessary, to leave any of the bone affected was exposing the patient to a risk which was unwarranted.

DR. ERIC PRICE said that he did not think that anyone had had a large experience with such cases. It was therefore desirable to pool their knowledge. His own experience made him pessimistic about the outlook in the case under discussion, even though at the present stage the result appeared to be satisfactory. There was quite a large indurated area at the lower and of the patient's left femur. It probably contained a large number of tumour cells in a fibrous tissue matrix. The theory outlined by Dr. Howard was good as far as it went, but a point to be remembered was that never at any time were all the cells simultaneously mitotic. Therefore a residuum of cells would survive therapy. One exposure killed some, but left others untouched. The experience from other cases in which he had been associated with Dr. Kaye Scott was that the condition was kept under control with increasing difficulty and threat to the skin, and often ultimately got out of control. The treatment necessary was the drastic one of rendering the tumour inactive with X-ray therapy, excluding after the lapse of time occurrence of secondaries, and then performing amputation. In a small series of cases which had come under his notice, difficulties had arisen, and that advice could not readily be put into operation for technical reasons. In one case the upper end of the femur had been involved and the patient died soon after the operation. In another in which the upper end of the femur was concerned, the bone had been completely disorganized by the growth, but the outline returned under the influence of the X rays. The patient refused operation, though the condition had relapsed. Dr. Price said that he was not aware of recovery in those cases. He had seen recovery after myeloma and chondrosarcoma. Finally Dr. Price said that surgery offered the best possibility of saving life in the particular instance being considered, and that the child would do best after disarticulation through the hip joint.

DR. ALAN PENINGTON said that it was a case in which their meagre knowledge of pathology should be applied clinically. Most malignant conditions were the result of a reaction of a carcinogen of unknown nature, and that applied in that particular instance. Dr. Penington said that he was not sure that it was not still present. Where a malignant condition was known to be present, and it was possible to remove it, a radical procedure appeared necessary.

DR. JOHN COLQUHOUN said that when Sir Gordon Gordon-Taylor was in Australia with the Royal Navy, he had given a lecture on amputations (fore and hind) for malignant conditions. Patients were treated with a survival period of five years and over. Dr. Colquhoun said that he was very impressed with the value of the surgeon's knife in that rather difficult disease. In London and Manchester, the surgeon played a prominent part in the treatment of osteogenic sarcoma. In Melbourne the tendency was to rely on radiotherapy and to forget that cures had been effected with radical surgery. It was very difficult to find reports of patients surviving after treatment by radiotherapy alone. The theory of action of radiotherapy was very pretty, but it was still not established beyond doubt whether radiotherapy for twelve months followed by surgery was the best method of attack, or whether a surgical attack should precede radiotherapy. Insufficient cases had been followed up to offer any definite conclusion. Sir Gordon Gordon-Taylor's observations suggested that surgery should come into the picture earlier. They could not be very proud of the results at the Children's Hospital in Melbourne, but in the future the best aproach might be more clearly elucidated. In the case of Dr. Howard's patient, Dr. Colquhoun said that he felt that operation should be urged and carried out at the hip joint. It would be interesting to follow the result, especially after a five-year period. Dr. Colquhoun said that he had shown a subject of "tumour" of the femur one year previously to the Pædiatric Society. The diagnosis had not been clear cut. The response to radiotherapy had been miraculous. Aspiration biopsy had revealed inflammatory tissue, and one month afterwards an abscess formed at the lower end of the femur and eventually discharged pus. The patient still had a uniform enlargement of the lower end of the femur, not unlike that of Dr. Howard's patient. In the case under discussion there appeared to be a sequestrum forming near the region of the aspiration biopsy. Time alone would determine whether they might be dealing with osteomyelitis in that particular case.

DR. MURRAY CLARKE said that the tumour was near the lower end of the femur. It would be rational to amputate at the optimum position which would be about five inches above the growth. The danger would be from metastasis by the blood stream and not by direct spread; but courage would be required, for if metastasis did develop, the surgeon might be blamed.

Dr. Howard, in reply, said that he remembered a medical patient being presented many years earlier on whom various speakers expressed a variety of views. A notable member of the society had got up and said that he would like to agree with all the other speakers. Dr. Howard said that he had felt the same till Dr. Clarke had spoken. He agreed that amputation was necessary, but they were dealing with such a dangerous disease that he felt that the whole of the affected bone should be removed. It was impossible to be certain how localized the tumour was. If metastasis did occur, one would feel disposed to blame the surgeon, and he did not feel courageous enough to take that risk.

Congenital Syphilis Treated With Penicillin.

DR. MEDWYN HUTSON showed a female infant who had first been seen on August 5, 1946, at the age of ten weeks. The mother had stated that a routine test at the Women's Hospital at the fifth month of pregnancy had disclosed that the result of the Wassermann reaction was positive. She had

been treated during the last four weeks of pregnancy with four injections of an arsenical, and then with twelve weekly injections of "Bismol".

The baby had appeared healthy at birth; she weighed six pounds seven ounces, and the result of a Wassermann test was negative. The mother had been advised that the test should be repeated in two or three months. The infant had remained well until, at the age of eight weeks, a severe cold developed, followed by a profuse nasal discharge. A rash appeared over the limbs and body one week later. The mother stated that she had never had any syphilitic lesion, but admitted the possibility of having contracted the disease before marriage. On examination, the baby had presented the typical picture of florid, well established congenital syphilis. She weighed eight pounds, and had a slightly wasted, atonic appearance. There was a muco-purulent nasal discharge, and the skin of the face was drawn, dry and wrinkled, and excoriated about the angles of the mouth and chin. A widespread maculo-papular rash was conspicuous, especially on the abdomen, buttocks, forearms and palms of the hands, and also on the soles. The lesions were about one-eighth of an inch in size and of a definite reddish brown or coppery hue. The liver and spleen were both considerably enlarged. The result of the Wassermann test was positive in a titre of 128. X-ray films showed an osteitis with rarefaction on the medial aspect of the upper tibial metaphysis, and bands of decreased density were present in the lower ends of the tibiæ.

It had been decided to begin treatment with penicillin, and 5000 units were given intramuscularly every three hours for fourteen days—a total of 550,000 units. The rash had disappeared fairly rapidly, and was hardly visible on the tenth day, and the wrinkled appearance of the face had cleared as the nasal discharge ceased. Ten days later the result of the Wassermann test was still positive in a titre of 64. A second course of 560,000 units of penicillin had then been given during fourteen days; and one week later the titre of the reaction had fallen to 32. A third course of penicillin, consisting on this occasion of 50,000 units twice daily, had then been given, the total dose being 990,000 units. In all a total of 2,000,000 units of penicillin had been given during the period of ten weeks in hospital. General progress had been uneventful, except for a temporary episode of fat dyspepsia, the baby regaining a normal appearance, and rapidly gaining in weight and vigour. On discharge from hospital at the age of five months, the baby had looked a very healthy bonny girl; she weighed eleven pounds eight ounces; the spleen could not be felt, although the liver was still palpable two fingers' breadth below the costal margin. At the age of six months her weight had increased to thirteen pounds seven ounces, neither the spleen nor the liver could be palpated, and X-ray films of the legs showed no evidence of the previous osteitis. The result of the Wassermann test was still positive in a titre of 2.

At that stage it had been decided to continue treatment with "Acetylarsan" and a weekly injection of one-half of a millilitre was given. Six weeks later, at the age of seven and a half months, the result of the Wassermann test was negative, and the Kahn test yielded a doubtful result. "Acetylarsan" was continued until ten injections had been given. At the time of the meeting the baby, aged ten months, appeared to be perfectly healthy, showed normal mental and physical development, and weighed twenty-four pounds.

Dr. Hutson said that the patient had been presented to illustrate several points. Firstly, it might be noted that florid congenital syphilis had appeared in the infant after regular and apparently adequate treatment of the mother during the latter four months of pregnancy. It would seem that more intensive treatment would have been desirable. Secondly, the infant had apparently been normal at birth, and the result of the serological test was negative. That was, of course, a well-known phenomenon, and indicated that close and repeated observation was necessary before an infant could be declared to be free from infection. The converse phenomenon of positive results to tests appearing in a non-syphilitic infant due to passive transfer of maternal reagin was also well known, and in those cases the quantitative reaction was of great value, as a rapidly falling titre might indicate that the infant was not in need of treatment, and would eventually prove to be non-syphilitic. Again, it was seen that penicillin in adequate dosage could be regarded as curative in at least some cases of congenital syphilis. So far relatively few patients had been treated, and no standard schedule of treatment could be laid down. Case reports in American literature had shown a wide variation in the amount of penicillin used, for example, doses of from 20,000 to 200,000 units per pound of body weight had been recommended. Most authors now appeared to favour the larger doses.

Whether the results were sufficiently good to warrant a change from standard conservative methods of treatment remained to be seen. There was little, if any, advantage from the point of view of economy in cost and time, but if the patient could be rendered permanently "sero-negative" with a fortnight's intensive treatment, it might be well worth while. Opinion was unanimous that open lesions healed very rapidly. In a recent American series of 22 patients treated, thirteen had become clinically well, with negative results to serological tests, four had shown sero-resistance, two had relapsed and four had died. Those were characteristic figures of the results being currently reported, and although the figures were not good, the authors did not believe that they would have been better had arsenicals and bismuth been used. Finally the value of the quantitative Wassermann test in following the course and results of treatment could be emphasized.

DR. CLIFFORD SAWREY then presented a male infant who had been admitted to the Children's Hospital on May 20, 1946, at the age of eight weeks. His weight at birth had been six pounds fifteen ounces. The history was one of vomiting, loss of weight and failure to thrive. The result of the Wassermann test on July 6, 1946, was strongly positive. He had had a purulent conjunctivitis for one month prior to admission. There was no history of a rash, jaundice or snuffles. On examination he was found to be a small but happy baby. There was a shallow ulcer on the hard palate. The liver and spleen were both enlarged. He had a slight bilateral conjunctival discharge, and the weight was six pounds twelve ounces. Treatment had been begun with half a millilitre of "Acetylarsan" administered intramuscularly each week. It was continued for ten weeks, and then a month's rest was allowed. On September 27, 1946, the result of the Wassermann test had been doubtful. A further ten weeks' course of "Acetylarsan", one millilitre weekly, had then been given, and on January 13, 1947, the result of the Wassermann test was negative. The baby had remained difficult with feedings, vomiting small amounts despite numerous trial feeding mixtures; he gained but four pounds in six months; on a lactone syrup milk feeding, however, he made rapid progress, and gained four pounds in the last six weeks before discharge from hospital. He had developed varicella and later morbilli, which was associated with intractable otorrhœa. He had been given penicillin 450,000 units in all, in doses of 5000 units intramuscularly every three hours for twelve days. This had cured the ear infection, and it was hoped that it would help permanently to alter the result of the Wassermann test. The child weighed fifteen pounds and was well on discharge from hospital at the age of nine months.

Dr. Sawry's second patient was a male infant, aged seven months. He had been admitted to hospital at the age of ten weeks with a history of having been born eight weeks prematurely, and weighing three pounds thirteen ounces. At the age of one week he had been jaundiced, but this subsided in a week. At the age of two weeks he had had an impetiginous sudaminal rash which also quickly cleared. At the age of five weeks he had again been observed to be jaundiced, and on that occasion it cleared slowly. At the age of eight weeks he had had a coppery rash on the body and legs. The result of the mother's Wassermann test was strongly positive, and both mother and child belonged to the O IV Rh-positive blood group. On examination, the baby had been found to be wizened in appearance. Snuffles was an obvious feature. The skin was peeling and a fading reddish brown macular rash was discernible. The liver was two fingers' breadth below the right costal margin. The result of the Wassermann test had proved to be positive at a titre of 64. X-ray examination of the bony skeleton had revealed periostitis of the long bones and irregular destruction of the frontal and parietal bones. The baby had been treated with 10,000 units of penicillin administered intramuscularly every three hours for ten days (approximately 100,000 units per pound). Progress had been slow but satisfactory, and the child gradually gained weight. On January 13, 1947, the result of the Wassermann test had been still positive at a titre of 32, by which time the liver had decreased in size. This illness had been complicated by varicella and pertussis with bronchopneumonia. On April 12, 1947, the result of the Wassermann test had been negative, and the child's weight was eleven pounds.

DR. HOWARD BOYD GRAHAM said that his experience with syphilis dated back twenty to twenty-five years. The physician was never able to be sure that antenatal treatment had been satisfactory. Every series showed that some babies had developed syphilitic changes. In Dr. Hutson's

patient treatment had been begun late in pregnancy and had been inadequate—too late and too little. Dr. Graham said that to obtain a positive result to the Wassermann test it was necessary to have an accumulation of a lot of Wassermann substance, or the test was a coarse rather than a fine one. It might take some weeks for sufficient Wassermann substance to accumulate; so a negative result shortly after birth could not be relied upon. Much arsenic and bismuth had been saved by allowing six weeks to elapse after a course of therapy before submitting the blood to examination. If a second series of injections were embarked upon as before, then much confusion arose. Some years previously it had been possible to divide a specimen and to send the blood from the same infant to two different laboratories, enabling the physician to have a check on the validity of the test. This might still be a desirable procedure. The titre method was by far the most helpful. Dr. Graham said that the reaction given by a baby with florid syphilis in the third month of life might be a much stronger one than usually encountered in acquired syphilis, indicating more widespread involvement, and probably necessitating more drastic treatment. Penicillin therapy for the disease was a recent innovation. He was thrilled to hear that it was being tried at the Children's Hospital. However, reliable cures could be observed with arsenic, bismuth and mercury, and admission to hospital was not necessary on that *régime*. The cost was so much less than that with penicillin that one doubted whether three-hourly injections over weeks and weeks offered a satisfactory substitute.

DR. KATE CAMPBELL commented on the unreliability of the serological tests for syphilis in the newborn. She said that she relied on X-ray pictures of the whole bony skeleton, which were much more informative.

DR. ROBERT SOUTHBY said that he was very interested in Dr. Hutson's patient's condition. It was a florid infection, and provided a good test for the efficacy of penicillin. The baby had been watched very closely and the clinical response had been dramatic. He therefore felt justified in urging the medical superintendent to persist with penicillin therapy in those cases. The result justified the experiment. The gradual reduction in titre, and eventually a negative result in the single case under discussion, were very encouraging. It was quite likely that the results would remain negative. No doubt arsenic could produce a similar result and bismuth alone would do it. The baby's mother did not have an intensive course of antisyphilitic treatment. The spirochætes had got a good start. Dr. Southby said that a negative result to the Wassermann test at birth in an infected baby was a well-known finding. Often no clinical manifestations were seen in the first two or three weeks. He agreed that a routine X-ray examination was more reliable in newborn babies.

DR. STANLEY WILLIAMS said that he wished to make one point. That was the justification for the further use of penicillin in the cases being considered. In assessing the reports, it was necessary to remember that a lot of penicillin used two or three years ago was not very potent, especially the American product, so it was too early to draw definite conclusions on the value of penicillin treatment. They had to remember that penicillin was free from side effects, but that could not be said of arsenic and bismuth. It was possible that the final answer lay in a combination of the three drugs.

In reply, Dr. Hutson said that treatment had been started in trepidation. It was possible that an excessive dosage had been used. The Americans had endeavoured to find out the minimum dosage. It was difficult to say whether penicillin was superior to all other methods, but it could be said that the open lesions healed more rapidly.

Correspondence.

PREFRONTAL LEUCOTOMY.

SIR: In reference to the recent papers in the journal on prefrontal leucotomy by Dr. H. M. Birch and others the following case may be worth recording. After the Suvla Bay disaster in 1915, it was my lot to be in charge of what was known as a "hospital carrier"—a ship that had shortly before been used for carrying horses and no doubt contained many tetanus organisms. Everything was very primitive and anything like operative treatment was out of the question. Among the hundreds of patients who came aboard at Suvla Bay was one who had a bullet wound, the entry and exit of which were symmetrically placed in each temporal region. The wounds were mere punctures inflicted several days previously and each was covered by a small dry scab. The man walked aboard seeming none the worse for his experience. His mentality appeared to be quite normal and his answers to questions were prompt and exact. But inquiry of his mates revealed that they were unanimous in thinking that he had become a very noticeably more cheerful person. It would seem likely that the bullet had performed a "prefrontal leucotomy"—possibly in the fastest recorded time. He was under observation for two weeks and remained quite well, but was then lost sight of.

Yours, etc.,

Ballow Chambers,
Wickham Terrace,
Brisbane.
October 27, 1947.

H. V. FOXTON.

THE NEW SOUTH WALES BRANCH AND THE GOVERNMENT PROPOSALS.

SIR: Last night I attended a special meeting of the New South Wales Branch to hear a report from the Council on its negotiations with Senator McKenna. As many people have noticed in themselves, I found that after the meeting there were questions I might have put, and comments I might have made, had I thought of them at the time; I now wish to present some aspects of the meeting which have since occurred to me.

During the whole meeting there was no appreciation of the reasons why the Federal Government are considering introducing a nationalized medical service. One speaker went so far as to make an extravagant analogy between the Prime Minister and Stalin, and the words "ruthless enemy" (of the profession) were used; Dr. Grieve's address (in contrast with that of Dr. Hunter) was one whose effect was obtained on an emotional level appealing to doctors "not to submit to blackmail".

In my consideration of the question of a national medical service I cannot forget that the Government has suggested that medical treatment should be adequate, universally available, and free to all. It has had this suggestion approved at an election and by a referendum. In my opinion it is a worthy one, and not impossible of achievement in a way satisfactory to doctors and still satisfy the progressive aim of the Government.

I have been disappointed that the Council has approached all conferences as a "reluctant dragon" instead of being a party willing to assist the Government to provide the best service possible with the resources of the profession limited as they are.

The reports, statements and resolutions of the Council arise from this incorrect, unprogressive attitude of theirs, and the technique of Dr. Grieve in not conducting last night's meeting in the usual manner (he refused to accept a motion which had been moved and seconded until three of his motions which at that stage of the meeting had not been moved nor seconded had been dealt with) leads me to think that he was determined to have last night's meeting "rubber stamp" his resolutions. He did not intend to present a report and let the meeting decide what should be done. Perhaps the meeting would have given the same decision as that he desired, but his bludgeoning methods are such that I, for one, object to strongly.

In my opinion it is regrettable that the profession has passed resolutions breaking off negotiations on the flimsy excuse that the scheme "would destroy private practice as we know it"; it is now our responsibility that there is no cooperation between us and the Government in bringing about what could be a progressive step both for the profession and the patient. We should, instead, be doing all we can to guide the Government and ensure the scheme's success.

Yours, etc.,

58, John Street,
Lidcombe,
New South Wales.
November 8, 1947.

IAN GARDINER.

SIR: There is a suggestion of something not straightforward on my part implied in the word "technique" used in Dr. Gardiner's letter, which is as out of place as was his suggestion, while speaking at the meeting, that Dr. Hunter in his address had probably not mentioned the idea that the Federal Council in its conference with the Minister had "wielded the big stick" before the Minister did. Nevertheless when Dr. Hunter and I pointed out to him the absence of substance in that suggestion, he did not withdraw it.

The meeting on the 7th instant was conducted by me in the usual manner, with Council business taking priority according to the notice convening the meeting. The meeting was called to hear the report from Council on the present position between the Association and the Government in respect of a nationalized medical service. The latter part of the Council's report consisted of three motions of policy to be submitted to members for their approval or disapproval. These motions were presented by me to the meeting and were truly before the meeting for a motion on them, when Dr. Stephania Siedlecky asked if I would accept a motion that a plebiscite should be held on the question of further negotiations with the Goverment. I asked whether there was a seconder and promptly Dr. Couani seconded. I then said I would accept the motion. A member then asked whether the business before the meeting was not the Council's three motions. I replied, "Yes", that I awaited a motion of approval or disapproval of them and that when that motion was dealt with I would put Dr. Siedlecky's motion. The meeting then carried motions of approval of the Council's "resolutions" by an overwhelming majority and rejected Dr. Siedlecky's motion in the same way.

This procedure was both correct and usual. The three resolutions referred to were not my resolutions, as stated by Dr. Gardiner, but the Council's. The procedure followed at this meeting was the same as that followed by a large number of different chairmen at 26 meetings of members in the country and five meetings in the metropolitan area. This was the first meeting at which objection was made to it.

It would become increasingly difficult to maintain the dignity of Association meetings if members should continue to use words and suggestions concerning the conduct of officers of the Association which belong to a world other than that of the Association.

As to the remainder of Dr. Gardiner's letter it is sufficient to state that the vast majority of those present at the meeting showed by their votes that they disagreed with it.

Yours, ec.,

H. R. R. GRIEVE.

135, Macquarie Street,
Sydney,
November 13, 1947.

JAUNDICE AND HYDATID CYSTS.

SIR: In a paper on "The Distribution of Measles (*Cysticercus bovis*) in African Bovine Carcasses" Mann and Mann (1947), *Veterinary Journal*, 103 (7), 239-251, have some interesting comments on the effects of jaundice on the cysticerci in muscles. These authors state that "jaundice . . . often causes evagination (of the scolex) *inside the bladder* (i.e. of the cyst) followed by hæmorrhagic infiltration of the bladder fluid with death of the measles. Jaundice due to East Coast Fever (a piroplasmosis) causes death of all measles within 7-10 days".

It would be extremely interesting to know whether the occurrence of "jaundice" in man has any adverse effect on the hydatid cyst (*Echinococcus*). If there was an effect it may open the way to a method of treatment of hydatid disease other than by surgical means, or by combined surgical and chemotherapeutic means such as by the injection of bile salts or pigments or their derivatives into the hydatid cyst.

The sheep would provide a suitable experimental animal for investigations of this problem.

Yours, etc.,

H. McL. GORDON,
Senior Research Officer.

McMaster Animal Health Laboratory,
Parramatta Road,
Sydney.
November 11, 1947.

THE NEW SOUTH WALES BRANCH PLEBISCITE

SIR: The referendum being conducted at present by the New South Wales Branch Council on alterations to its constitution has been conducted in a manner rather suggestive of that adopted by our Federal Parliament in its recent referenda. The case for both sides of the question has been put by Council itself, although it is definitely a supporter of one side; and it has been put in a somewhat biased manner. This is hardly democratic.

The ordinary voter is not conversant with the undercurrents that have been the cause of alternative proposals being submitted, and he is likely to have used, as his sole guide in voting, the brochure enclosed with his ballot paper.

In the preamble of this brochure it is not made clear why Council should see fit to submit an alternative scheme, after having been a party to the discussions with the special committee appointed to inquire into the matter. This committee had apparently twice, by majority vote, signified its approval of scheme (*a*).

It is also not sufficiently made clear that in scheme (*b*), proposed by Council, the candidate elected to represent, for example, the public medical service, will not in fact be elected by his peers, but by the general body of voters, most of whom will be ignorant of the respective merits of candidates standing as representatives of such special branch of medicine.

It is therefore suggested that, whatever the result of the plebiscite, there are strong grounds for regarding the findings as invalid. It would be more democratic to hold a further referendum after both sides of the case have been submitted to electors in a more democratic manner.

Yours, etc.,

EDWARD S. STUCKEY.

57, Spit Road,
Mosman,
New South Wales.
November 10, 1947.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Annual General Course.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that Dr. Geoffrey S. Todd, C.V.O., O.B.E., will give a lecture on "Diseases of the Chest in General Practice" on Wednesday, December 3, 1947, at 4.30 p.m. in the Stawell Hall, 145, Macquarie Street, Sydney. Dr. Todd is Medical Superintendent of the King Edward VII Sanatorium, Midhurst, England, Honorary Consultant in Tuberculosis to the British Army and Chest Consultant to the Royal Air Force.

Course in Pædiatrics.

A course in pædiatrics will be held at the Royal Alexandra Hospital for Children from December 8 to 9, 1947, and will be made up as follows:

Monday, December 8.—9.30 a.m., "Bronchitis and Bronchiectasis" (Dr. Raymond Green); 11.45 a.m., "Empyema" (Dr. T. Y. Nelson); 2 p.m., "Acute Rheumatism" (Dr. W. P. MacCallum); 4 p.m., "Anæsthesia in Childhood" (Dr. A. Distin Morgan).

Tuesday, December 9.—9.30 a.m., "Artificial Feeding of Infants" (Dr. Lorimer Dods); 11.45 a.m., orthopædic demonstration (Dr. Lawrence MacDonald); 2 p.m., "Acute Nephritis" (Dr. Lorimer Dods); 3.15 p.m., "Convulsions of Infancy and Childhood" (Dr. D. G. Hamilton).

Wednesday, December 10.—9.30 a.m., "Renal Tract Infections of Infancy and Childhood" (Dr. J. W. S. Laidley); 11.45 a.m., "Nutritional Problems" (Dr. K. Winning); 2 p.m., "Osteomyelitis" (Dr. J. Steigrad); 3.15 p.m., demonstration of nursing procedures (Sister O. Ring).

Thursday, December 11.—9.30 a.m., "Care of Premature Infant" (Dr. K. Winning); 11.45 a.m., "Croup and Allied Conditions" (Dr. Joan Tom); 2 p.m., follow-up clinic (Dr. T. Y. Nelson); 3.15 p.m., "Intradermal Tests" (Dr. D. Reye).

Friday, December 12.—9.30 a.m., "Intravenous Fluids in Pædiatric Practice" (Dr. Lorimer Dods); 11.45 a.m., intravenous infusion demonstration (Dr. Joan Tom); 2 p.m., "Abdominal Pain Associated with Surgical Conditions in Infancy and Childhood" (Dr. T. Y. Nelson); 3.40 p.m., surgical clinic.

Saturday, December 13.—9.30 a.m., "Vomiting in Infancy" (Dr. K. Winning); 10.45 a.m., "Pyloric Stenosis" (Dr. J. Steigrad).

Monday, December 15.—9.30 a.m., "Appropriate Ages for Operations" (Dr. T. Y. Nelson); 11.15 a.m., allergy clinic (Dr. S. E. L. Stening); 2 p.m., medical and surgical outpatient clinics.

Tuesday, December 16.—9.30 a.m., "Meningitis" (Dr. Lorimer Dods); 11.45 a.m., "Immunization Against Diphtheria and Pertussis" (Dr. Stephen Williams); 2 p.m., "Diagnosis and Clinical Features of Poliomyelitis" (Dr. W. P. MacCallum); 3.45 p.m., surgical clinic.

Wednesday, December 17.—9.30 a.m., bronchiectasis clinic; 11.45 a.m., "Minor Surgical Procedures" (Dr. E. Stuckey); 2 p.m., "Blood Dyscrasias of Infancy and Childhood" (Dr. Lorimer Dods); 3.15 p.m., orthopædic demonstration (Dr. Lawrence MacDonald).

Thursday, December 18.—9.30 a.m., "Common Ear, Nose and Throat Problems" (Dr. N. Meacle); 11.45 a.m., "Breast Feeding" (Dr. K. Winning); 2 p.m., "Intrathoracic Tuberculosis" (Dr. W. P. MacCallum); 3.30 p.m., "Poliomyelitis: General Principles of Posturing and Reeducation of Affected Muscles" (Dr. A. Armstrong).

Friday, December 19.—9.30 a.m., "Pink Disease" (Dr. D. Vickery); 11.45 a.m., "Blood Dyscrasias of Infancy and Childhood" (Dr. Lorimer Dods); 2 p.m., dermatological demonstration (Dr. George Norrie); 3.15 p.m., "Intussusception" (Dr. J. Steigrad).

The fee for the course is £5 5s. and early application should be made to the Course Secretary, 131, Macquarie Street, Sydney. Telephones: BW 7483-B 4606.

Hospitals.

CENTENARY OF THE ROYAL MELBOURNE HOSPITAL.

THE centenary of the Royal Melbourne Hospital will be celebrated in 1948. Part of the celebrations will take the form of a scientific session from March 1 to 10. For this scientific session the following provisional programme has been drafted.

Monday, March 1.

8 p.m.—Inaugural address—the Right Honourable R. G. Casey, C.H., D.S.O., M.C. (Wilson Hall, University of Melbourne): "Health Problems in India."

Tuesday, March 2.

9.15 a.m.—Dr. Clive Fitts: "Congenital Heart Diseases." Mr. Henry Searby: "Thyreoid Surgery." Dr. E. G. Robertson: "Lesions of the Brain Cell and Encephalography."

11.30 a.m.—Dr. Hume Turnbull: "Management of Patients After Acute Coronary Lesions."

2 p.m.—Mr. G. R. A. Syme: "Treatment of Varicose Veins." Dr. J. H. Kelly: "Modern Therapy in Dermatology." Dr. Gardner: "Clinical Pathology including Hæmatology and Bacteriology." Miss Splatt: "Clinical Biochemistry: Technique of Diagnostic Laboratory Methods."

4 p.m.—Dr. W. G. D. Upjohn: "Forty Years of Surgery in the Melbourne Hospital."

8 p.m.—Sir Hugh Cairns: Lecture.

Wednesday, March 3.

9.15 a.m.—Dr. G. A. Penington: "Colitis." Mr. W. E. A. Hughes-Jones: "Surgery of Peptic Ulcer." Mr. B. T. Keon-Cohen: "Treatment of Compound Fractures."

11.30 a.m.—Professor P. MacCallum: "Twenty-Five Years of Pathology at the Melbourne Hospital."

2 p.m.—Mr. E. E. Dunlop: "Upper Gastric and Œsophageal Carcinomata." Mr. R. S. Hooper: "The Common Head Injury and its Complications" (Sir Hugh Cairns will be present).

4 p.m.—Mr. Victor Hurley: "The Diagnosis and Treatment of Lumps in the Breast."

8 p.m.—Dr. Wm. Evans: "Heart Sounds."

Thursday, March 4.

9.15 a.m.—Mr. A. E. Coates: "Pain and the Surgeon." Dr. L. E. Rothstadt: "Some Pathological and Clinical Aspects of Cardio-Aortic Syphilis." Dr. A. J. M. Sinclair: "The Integration of Psychological and General Medicine."

11.30 a.m.—Professor F. M. Burnet: "Mucins and Mucoids in Medicine."

2 p.m.—Demonstration in the Walter and Eliza Hall Institute. Mr. B. K. Rank: "Reparative Surgery of Industrial Injuries."

2 p.m.—Mr. J. Hayward: "Diseases of the Lung." Dr. W. T. Coyle: "Treatment of Early Venereal Disease."

4 p.m.—Professor R. D. Wright: "Recent Findings about Reflex Action."

8 p.m.—Sir Alan Newton: "Development of Thyreoid Surgery in Melbourne."

Friday, March 5.

9.15 a.m.—Dr. K. D. Fairley: "Disorders of the Thyreoid Gland." Mr. John Shaw: "Clinical Demonstration of Cases." Mr. R. S. Hooper: Ward round.

11.30 a.m.—Mr. W. A. Hailes: "Treatment of the Paralysed Bladder." 2 p.m.: Clinico-pathological demonstration.

4 p.m.—Dr. Ivan Maxwell: "Allergy of the Respiratory Tract."

8 p.m.—Dr. Wm. Evans: "Heart Murmurs."

Monday, March 8.

9.15 a.m.—Dr. Wm. Evans: Ward rounds. Royal College of Obstetricians: W. J. Rawlings, "Medical Aspects of Dysmenorrhœa"; D. F. Lawson, "Anuria in Obstetrics". Mr. Orm Smith: "Surgery of the Gastro-Intestinal Tract." Dr. R. Kaye Scott: "Radiotherapy in Cancer."

11.30 a.m.—Dr. Douglas Thomas: "Gastric Emptying."

2 p.m.—Operative demonstration (Royal College of Obstetricians): Mr. L. W. Gleadell, "Spalding Richardson's Composite Operation". Mr. R. S. Hooper: "Lesions of the Optic Pathway." Dr. L. E. Hurley: "Diagnosis of Gastric Jaundice and Hepatitis." Mr. H. H. Eddey: "Carcinoma of the Colon."

4 p.m.—Professor H. Dew: "Research Activities of the Department of Surgery, University of Sydney."

8 p.m.—Dr. Wm. Evans: "Heart Pain."

Thursday, March 9.

9.15 a.m.—Dr. Crisp and Dr. Barbara Wood: "Hyperparathyreoidism and other Radiological Demonstrations." Mr. J. Grayton Brown: "Treatment of Epithelioma and Rodent Ulcer."

11.30 a.m.—Dr. K. F. Russell: "The Early Surgeons of the Royal Melbourne Hospital, 1847-1900."

2 p.m.—Dr. J. H. Bolton: "Hæmolytic Anæmia and Pernicious Anæmia." Mr. J. B. Turner: "The Surgical Management of Bleeding from the Bowel." Dr. T. a'B. Travers: "Corneal Transplants." Dental demonstrations and lectures.

4 p.m.—Mr. Orm Smith: "Surgery in Peptic Ulcer."

8 p.m.—Dr. L. Hurley: "The Place of the Clinical History in Medicine."

Wednesday, March 10.

9.15 a.m.—Dr. Wood: "Chronic Diseases of the Liver." Mr. H. Moore: "Genito-Urinary Tuberculosis." Anæsthetists: "Modern Anæsthetic Drugs and Methods."

11.30 a.m.—Professor Sunderland: "Trends in Anatomical Research."

2 p.m.—Dr. Ivan Maxwell: "Toxic Goitre." Mr. T. H. Ackland: "The Surgical Treatment of Common Anal Diseases." Dr. L. T. Wedlick: "The Value of Physical Medicine in Modern Treatment."

4 p.m.—Professor S. Rubbo: "Infection: A Hospital Problem."

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Cameron, John, M.B., B.S., 1944 (Univ. Sydney), 9, Jersey Road, Strathfield.

Merory, Paul Heinz, L.R.C.P. (London), M.R.C.S. (England), 1947, D.O.M.S. (England), 1946, registered in accordance with the provisions of Section 17 (*b*) of the *Medical Practitioners Act*, 1938-1945, 182, Victoria Road, Bellevue Hill.

Carmody, Frank Spohn, M.B., B.S., 1945 (Univ. Sydney), 3, Fisher Avenue, Vaucluse.

Rugless, Margaret, provisional registration, 1947 (Univ. Sydney), 8, Seaview Street, Randwick.

Baker, Cecil Horace, provisional registration, 1947 (Univ. Sydney), Hornsby and District Hospital, Hornsby.

Sabiel, Kevin Norman, provisional registration, 1947 (Univ. Sydney), Grafton Base Hospital, Grafton, New South Wales.

The undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Barlow, Marguerite Mora, M.B., B.S., 1947 (Univ. Adelaide), 36, Portrush Road, Tusmore.

Godfrey, Edward John Owen, M.B., B.S., 1945 (Univ. Adelaide), 17, Devonport Terrace, Hazelwood Park.

O'Brien, John Alexander, M.B., B.S., 1947 (Univ. Adelaide), Royal Adelaide Hospital, Adelaide.
Mellor, Geoffrey Lloyd, M.B., B.S., 1947 (Univ. Adelaide), 5, Bedford Street, Kensington Park.

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association:

Bialoguski, Michael, provisional registration, 1947 (Univ. Sydney), 226, Sydney Road, Balgowlah (as from January 1, 1948).
Butler, John Ferdinand, M.B., B.S., 1945 (Univ. Sydney), Cox Street, Bellbird, New South Wales (as from January 1, 1948).
Cameron, John, M.B., B.S., 1944 (Univ. Sydney), 9, Jersey Road, Strathfield (as from January 1, 1948).
Degotardi, John Charles, provisional registration, 1947 (Univ. Sydney), Eucalyptus Street, Gordon, New South Wales (as from January 1, 1948).
Finley, Adrian Geoffrey, M.B., B.S., 1944 (Univ. Sydney), 5, Shellbank Parade, Cremorne (as from January 1, 1948).
Merory, Paul Heinz, registered in accordance with the provisions of Section 17 (*b*) of the *Medical Practitioners Act*, 1938-1945, 182, Victoria Road, Bellevue Hill (as from January 1, 1948).
Oliver, John, M.B., B.S., 1947 (Univ. Sydney), Sydney Hospital, Sydney (as from January 1, 1948).
Sheppard, Vincent Earle Moxey, provisional registration, 1947 (Univ. Sydney), Lammerburn, New River Road, Emu Plains, New South Wales (as from January 1, 1948).
Crane, Enid Nance, M.B., B.S., 1947 (Univ. Sydney), 38, Herbert Street, Rockdale.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association:

Derrington, Arnold Ward, M.B., B.S., 1947 (Univ. Adelaide), 74, Northumberland Avenue, Tusmore.
Thomson, Theodore Roderick, M.B., B.S., 1947 (Univ. Adelaide), Royal Adelaide Hospital, Adelaide.
Randell, William Richard, M.B., B.S., 1947 (Univ. Adelaide), Royal Adelaide Hospital, Adelaide.
Jones, Geoffrey Hedley, M.B., B.S., 1947 (Univ. Adelaide), 15, Burke Street, Tusmore.
Cheek, Donald Brook, M.B., B.S., 1947 (Univ. Adelaide), 26, Fitzroy Terrace, Prospect.
Miller, Robert Lionel, M.B., B.S., 1947 (Univ. Adelaide), 6, Daphne Street, Prospect.
Lennard, Lancelot Barrett, M.B., B.S., 1947 (Univ. Adelaide), St. Leonards, Kondut, Western Australia.
Russell, Janet Barbara, M.B., B.S., 1947 (Univ. Adelaide), Napier Terrace, Westbourne Park.

Medical Appointments.

Dr. J. V. Hynes has been appointed medical officer, Brisbane Mental Hospital, Goodna, in pursuance of the provisions of *The Public Service Acts*, 1922 *to* 1945, of Queensland.

Books Received.

"Mental Health: A Practical Guide to Disorders of the Mind", by John H. Ewen, F.R.C.P.E., D.P.M., with a chapter on Special Treatments and their Practical Technique", by C. Friedman, M.D. (Vienna), L.R.C.P. and S. (Edinburgh); 1947. London: Edward Arnold and Company. 8½" × 5½", pp. 270. Price: 12s. 6d.

"Progress in Gynecology", edited by Joe V. Meigs, M.D., and Somers H. Sturgis, M.D.; 1947. London: William Heinemann (Medical Books), Limited. 9" × 6", pp. 566, with many illustrations, some of them coloured. Price: 35s.

"Psychopathology: A Survey of Modern Approaches", by J. Ernest Nicole, O.B.E., L.M.S.S.A., D.P.M.R.C.P. and S.; Fourth Edition; 1946. London: Baillière, Tindall and Cox. 8½" × 5½", pp. 278. Price: 15s.

"The Doctor's Job", by Carl Binger, M.D.; 1947. London: George Allen and Unwin, Limited. 8½" × 5½", pp. 244. Price: 12s. 6d.

"Internal Medicine in General Practice", by Robert Pratt McCombs, B.S., M.D., F.A.C.P.; Second Edition; 1947. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9¼" × 6¼", pp. 758, with many illustrations, some of them coloured. Price: 56s.

"Poisons: Their Isolation and Identification", by Frank Bamford, B.Sc.; Second Edition revised by C. P. Stewart, M.Sc., Ph.D., with a foreword by Professor Sydney Smith, C.B.E., M.D., F.R.C.P.; 1947. London: J. and A. Churchill, Limited. 8½" × 5½", pp. 312, with illustrations. Price: 21s.

"The Medical Clinics of North America", July, 1947, issue (issued every two months); 1947. Philadelphia and London: W. B. Saunders Company, Limited. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. Mayo Clinic Number. 9" × 5¾", pp. 286, with illustrations. Price: Annual subscription, £5 10s. (cloth binding), £4 12s. 6d. (paper binding).

Diary for the Month.

Nov. 25.—New South Wales Branch, B.M.A.: Ethics Committee.
Nov. 26.—Victorian Branch, B.M.A.: Council Meeting.
Nov. 27.—New South Wales Branch, B.M.A.: Branch Meeting.
Nov. 28.—Queensland Branch, B.M.A.: Council Meeting.
DEC. 2.—New South Wales Branch, B.M.A.: Executive and Finance Committee. Organization and Science Committee.
DEC. 3.—Western Australian Branch, B.M.A.: Council Meeting.
DEC. 3.—Victorian Branch, B.M.A.: Branch Meeting.
DEC. 3.—Victorian Branch, B.M.A.: Council Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute; Brisbane City Council (Medical Officer of Health). Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

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